Essays on Managing Healthcare Ecosystems

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Preface

Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. I further state that no substantial part of my thesis has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee.

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Abstract

From medical services, community and social care, organ transplantation and blood supply chains, to pharmaceutical innovation, research and development, and manufacturing and distribution, the healthcare ecosystem is wide ranging in both its functions and stakeholders. This dissertation aims to better understand, evaluate, and address major challenges and inefficiencies in this complex system. Through the utilization of operations management concepts, strategies, and methodologies, the dissertation derives and offers insights for key decision–makers and practitioners.

The first half of the dissertation lays the groundwork by characterizing healthcare supply chain management and provides a framework that adapts and applies supply chain thinking to the healthcare domain. In the second half of the dissertation, the research focuses in on the pharmaceutical industry and, particularly, to examining recent and major trends in clinical development: the changing nature of clinical research outsourcing, and the decentralization of trials. These trends are assessed by considering the key stakeholders in the ecosystem and the intricacies of their interactions. The main chapters are summarized below.

Healthcare supply chains are categorized into four main categories with the primary strategies, challenges, and risks as well as the existing research for each category discussed. For each supply chain, Chapter 2 details at least one efficient and effective strategy that has been used in practice and includes a short discussion on future research.

With a focus on healthcare delivery, Chapter 3 offers a primer on supply chain thinking in healthcare, by following a framework that is customer focused, systems based, and strategically orientated and that simultaneously considers clinical, operational, and financial dimensions. The

goal is to offer an understanding of how concepts and strategies in supply chain management can be applied and tailored to healthcare by considering the sector's unique challenges and opportunities.

Pharmaceutical (pharma) companies face substantial financial consequences from clinical trial overruns. To offer an analytical perspective on how pharma managers' choice of outsourcing relationship type with contract research organizations (CROs) can affect clinical development timelines, Chapter 4 explores strategic partnerships (characterized by a pharma company's commitment of future business to CROs) and transactional arrangements (one–off but potentially repeated engagements). The problem is formulated as a three–stage game between a pharma company and CRO. The *when* and *how* of strategic partnerships are investigated through the characterization of the conditions under which a pharma company should pursue a strategic partnership with a CRO rather than engage in a transactional arrangement, and in detailing the way that these relationships unfold.

The COVID–19 pandemic exposed the vulnerabilities of a conventional site centric clinical trial design and spurred the adoption of decentralized clinical trials (DCTs), trials wherein recruitment and data collection are not restricted to one centralized location. There has been a growing interest in understanding how DCTs can mitigate existing challenges in clinical development, particularly regarding sponsor, site, and participant burdens. Chapter 5 provides an overview on DCTs, emphasizing how they fit into and alter the current clinical development landscape. The chapter puts forward a conceptual framework that employs systems thinking to evaluate the impact of trial decentralization on the ecosystem through a reiterative assessment of stakeholder pain points.

Dedication

To my mother, who has been there for me every step of the way.

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Conferences

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*Presenting author indicated in **bold** font.*

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Chapter 1

General Introduction

1.1 Motivation

I have always had a profound curiosity towards the healthcare and pharmaceutical industries. Throughout the past four years, I have been able to explore the business realm of healthcare through my research. The choice of topic for this dissertation was motivated by the increasing complexity of managing healthcare ecosystems. Complexities prevail in the various actions and activities that are required to ultimately deliver quality care to patients and they may exacerbate and pose significant challenges to practitioners and decision–makers. To wade through such complexities, one needs to carefully consider the many interacting elements of the ecosystem. This is achieved through *systems thinking* which refers to the ability to take a "whole system" perspective when thinking about problems and their solutions (Behl and Ferreira 2014). The essays in the dissertation follow this overarching approach in attempting to tackle major issues in healthcare. The initial half of the dissertation studies the wider healthcare ecosystem and the main challenges and risks faced by different healthcare supply chains. Building on the concepts and learnings of the first two chapters, the second half of the dissertation focuses specifically on the pharmaceutical industry and explores two cases where recent developments (the changing nature of outsourcing relationships and trial decentralization) have complicated critical stakeholder decisions for clinical development.

Several inherent factors contribute to the difficulty in managing healthcare ecosystems. Unlike most typical goods and services, healthcare can be a sensitive subject as the health of a human being is at stake. Not surprisingly, both the healthcare and pharmaceutical industries are highly regulated. Operating under the guiding principle of *"do no harm",* stakeholders tend to express a degree of risk aversion and sometimes resist change. Although healthcare is co–productive in nature and patients are the ultimate consumers of healthcare services, they delegate their healthcare "purchasing decisions" to healthcare providers. These "purchases" are paid for by third parties

(such as insurance providers or the government). Such delegated decision-making and third–party financing can lead to inefficiencies, power imbalances and information asymmetries. Further complicating matters is the fact that healthcare is a merit good (a type of good which, when consumed, provides external benefits (economicsonline.co.uk)) and a credence good (a type of good with qualities that cannot be observed by the consumer after purchase (investopedia.com)). Stakeholders may thus find it difficult to quantify and assess the value or utility of healthcare services. This has wide-ranging consequences for performance metrics, incentive mechanisms and payment methods in healthcare.

Perhaps one of the greatest challenges to healthcare is the fact that the world's population has been increasing and aging. The number of people aged 65 and over is growing three times faster than the number of people under 65 (Charlesworth and Johnson 2018). Consequently, countries are spending a significant proportion of their gross domestic product on healthcare. There is also a rising burden of disease as more individuals are living with a chronic disease and, globally, one in three adults lives with more than one chronic condition (Hajat and Stein 2018), such as arthritis, diabetes, and mental illness. Chronic diseases deteriorate individuals' health, reduce life expectancy, and degrade quality of life. Care for the chronically ill is also costly; in the United States, chronic disease accounts for nearly 75% of aggregate healthcare spending (Raghupathi and Raghupathi 2018). Therefore, the need to contain costs while ensuring quality care is evident. Unfortunately, a well–documented inefficiency in healthcare is the pervasiveness of fragmented care. Fragmentation in healthcare systems is costly, leading to wastes (e.g., duplication of services) and unrealized value in care delivery. For instance, as life expectancy increases, addressing fragmentation between medical services, community and social care will become critical to the holistic management of patient needs (National Collaboration for Integrated Care and Support 2013). Systems thinking and supply chain management lend themselves as natural approaches for assessing and combating fragmentation in healthcare systems.

The healthcare industry has also been grappling with the challenges of tackling health inequalities (which are avoidable, unfair, and systematic differences in health between different groups of people (Williams et al. 2022)) and increasing diversity in healthcare research and delivery. Patients

have also become more vocal in expressing their demands, preferences, and expectations (for instance, increased expectations of greater convenience of care (Sommer et al. 2018)). This has led to a heightened focus on patient centricity (an approach that seeks to treat the patient rather than the disease) and patient engagement (the effort and movement to amplify and address patient voices) in healthcare. Such efforts have given rise to trends like moving the sites of care closer to patients' homes and the decentralization of clinical trials. The flexibility and convenience of these models may also impact patient compliance and adherence, thereby improving the quality of care (Sommer et al. 2018, Van Norman 2021). Aside from improvements in the care provided, patient experience, accessibility and representation, these shifts may offer potential cost advantages. However, such models place new demands and pressures onto existing systems and stakeholders, and the impact of their deployment needs to be carefully assessed through a systems approach.

Another trend changing the healthcare landscape is the advancement and increased industry uptake of healthcare technologies. Furthermore, the COVID–19 pandemic has helped improve attitudes toward digital health solutions and has heightened stakeholder comfort levels with digital technologies. According to research by McKinsey, telehealth utilization in 2021 was 38X higher than before the pandemic. The analysis also shows that 58% of physicians continue to view telehealth more favorably now than they did before COVID–19, and 40% of consumers believe they will continue to use telehealth compared to just 11% using telehealth prior to the pandemic (Bestsennyy et al. 2021). These shifts are accompanied by growing industry investments in developing and bolstering IT infrastructure. According to Grand View Research, the global digital health market (valued at USD 175.6 billion in 2021) is projected to grow at a compound annual growth rate of 27.7% by 2030 (Grand View Research 2022). The proliferation of electronic health records, wearable technologies, and online healthcare platforms have also generated large amounts of data. The surge in data availability, in conjunction with growing computer power, has allowed healthcare analytics tools, such as AI and machine learning, to play an expanding role in the advancement of healthcare. However, the growing utilization of healthcare technologies and health data has raised questions regarding data security, the interpretability, accuracy, use and value of data, and the interoperability of systems, among others. Moreover, the emergence of and growing demand for new stakeholders (e.g., technology vendors) and new stakeholder roles (e.g., data scientists) involved in health research and healthcare provision calls for systems thinking in

assessing the impact of digital transformation in healthcare. There are many other challenges faced by healthcare systems; a healthcare workforce crisis[1], ever–increasing healthcare expenditure[2], rise in clinical trial complexity[3], longer clinical trial timelines[4], and rising R&D costs[5], to name a few.

All these factors and recent developments complicate the management of healthcare systems. The broader healthcare ecosystem encompasses various subsystems (such as healthcare delivery and pharmaceuticals) and many different stakeholders, each with their own attributes, goals, constraints, and risks, which play a unique but interrelated role. Employing operations management strategies and methodologies, the dissertation studies major challenges in health systems, while addressing and building on several central themes.

1.2 Central Themes

Systems thinking

A system is a group of interacting or interdependent elements forming a unified whole (Merriam–Webster 2022). These elements can be "people, processes, information, organizations, and services, as well as software and other systems, that when combined, have qualities that are not present in any of the elements themselves" (Royal Academy of Engineering et al. 2017). A key

[1] The WHO estimates a projected shortfall of 10 million health workers by 2030 (WHO 2022).

[2] Over the last five decades, health spending in the US has increased from 353 USD per person in 1970 to 12,531 USD in 2020 on a per capita basis (Kurani et al. 2022).

[3] Research from the Tufts Center for the Study of Drug Development found that the average number of distinct Phase II and III protocol procedures increased 44% since 2009, and the average number of investigative sites conducting such phases increased 33% from 2009-2012 to 2017-2020 (GlobeNewswire 2021).

[4] According to another study from the Tufts Center for the Study of Drug Development, FDA approved drugs and biologics spent 89.8 months, on average, in clinical trials between 2014 and 2018 as compared to 83.1 months, on average, between 2008 and 2013 (Passut 2020).

[5] In 2019, the pharmaceutical industry spent 83 billion USD on research and development, 10X what it spent per year in the 1980s (Congressional Budget Office 2021).

component of a system is that a system is not simply a collection of its individual elements, but rather, it is more than the sum of its parts (Meadows 2008). Systems thinking is thus the ability to take a "whole system" perspective when thinking about problems and their solutions (Behl and Ferreira 2014). Since the coining of the term by Barry Richard in 1987, "systems thinking" has taken on various definitions (see Arnold and Wade (2015) for a review of the literature). Many different systems thinking tools have emerged (e.g., root cause analysis, behavior over time graphs, and system dynamics[6], to name a few; see Monat and Gannon (2015) for a discussion of tools). One can thus better understand complex problems by considering interconnectedness and interrelationships through systems thinking (Sterman 2000). Consequently, systems thinking has been applied in numerous domains, including healthcare[7].

Supply chain management

A supply chain (SC) is a "network of organizations that are involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services in the hands of the ultimate consumer" (Christopher 2016, p. 13). Supply chain management is the "management of upstream and downstream relationships with suppliers and customers in order to deliver superior customer value at less cost to the supply chain as a whole" (Christopher 2016, p. 3). Every supply chain is a system of organizations, materials, resources (including human capital), activities, information, and finances that help move a product or service from suppliers to end customers/consumers while optimizing end–to–end efficiency and effectiveness. As a result, to match customer requirements with supply constraints, supply chain management, as a management strategy, is characterized by a *systems approach* (i.e., considers the organizations in the SC as an end–to–end, integrated entity), a *strategic orientation* (i.e., aligns

[6] During the COVID-19 pandemic, I became familiar with system dynamics and, alongside other academics, employed the methodology to better understand the state of the pandemic and to forecast bed capacity demand for trusts in the East of England. The work was conducted to support and inform decision-making in regional health systems.

[7] A recent and relevant application of systems thinking is the "Engineering Better Care" framework co-developed by the Royal Academy of Engineering, the Royal College of Physicians, and the Academy of Medical Sciences. This systems approach framework considers four interrelated perspectives (people, systems, design, and risk) to evaluate health and care design and improvement initiatives through an iterative and systematic way (Royal Academy of Engineering et al. 2017).

the intra– and interfirm goals and capabilities with those of the SC), and a *customer focus* (i.e., focuses on customer value as the key driver of the supply chain's activities) (Mentzer et al. 2001).Although historically healthcare SCs have typically been associated with the procurement and logistics of healthcare supplies and services (see de Vries and Huijsman (2011) and Kim and Kwon (2015) for a reviews on the management of healthcare supplies), the dissertation adopts a broader definition of healthcare supply chain management: the management of people, processes, information and finances to deliver medical products and services to consumers, with the aim of improving clinical outcomes and patient and provider experience, while controlling costs (Berwick et al. 2008, de Vries and Huijsman 2011).

Outsourcing and collaboration

Research in the dissertation also relates to operations management work in outsourcing. On a broad level, this line of work has explored incentives and contracting between an outsourcer and contractor(s) and examines how clients can use various contract terms and levers to influence contractors' efforts. In the context of service outsourcing, literature has evaluated commonly employed industry contracts. Research has looked at how to design outsourcing contracts to ensure timely and quality services from providers. For instance, Zhang et al. (2018) examine a service provider's optimal pricing and operational strategy under two commonly used pricing schemes (hourly–rate contract and two–part tariff) in an environment characterized by double–sided asymmetric information. Feng et al. (2019) solve for the optimal outsourcing contract that minimizes the client's total cost and show that the optimal contract depends on the relationship between the service provider's capacity and quality costs.

Closely adjacent to this literature is a substantial amount of research on project management of outsourced work. This line of research investigates various incentive schemes that a client or project manager can use to reduce the completion time of outsourced projects by influencing contractors' determination of their work rates. For instance, Bayiz and Corbett (2005) derive the first–best, optimal fixed price and linear incentive contracts for parallel and serial tasks. Kwon et al. (2010) consider the impact of contracts with delayed payments on suppliers' work rates while Vairaktarakis (2013) analyzes manufactures' subcontracting strategies so as to minimize their

overall completion time. Chen et al. (2015) propose an incentive contract for serial stochastic projects and compare it to a fixed payment contract, a lower–bounded payment contract, and a dynamic contract, as well as two payment timing options. Kwon et al. (2010b) consider channel coordination across contracts in project supply chains by examining nonlinear contracts and demonstrate that time–based and cost–sharing contracts can coordinate the project, while Chen and Lee (2017) show that channel coordination can be achieved via a delivery schedule–based contract. Dawande et al. (2019) derive optimal contracts between a principal and multiple agents for parallel and sequential projects, and the simplicity of their contracts illustrates that complex contracts are not necessary for maximizing contracts. Our work also relates to collaboration in projects. Many knowledge intensive projects such as research and development of pharmaceuticals are characterized by an uncertain timeline and outcomes, necessitate a flexible scope, and often require co–production between a client and service provider. With collaboration, both parties take actions (for instance, by exerting costly effort or risk sharing) to achieve an outcome (such as expediting the completion time of a project). Take, for example, Rahmani et al. (2017) who characterize the collaborative work dynamics between a client and a vendor working to complete a project with a finite deadline. The authors demonstrate various effects on the level of effort exerted by both parties based on how much progress has been made, how close the deadline is, and how close the project is to completion. They also examine the issue of free riding. In a similar vein, Song et al. (2021) study gaming in collaborative risk–sharing partnerships for joint projects and discuss mitigation strategies to incentive issues.

Incentives and performance–based contracting

Across many manufacturing and service industries, performance–based contracting (PBC) has been employed to govern buyer–supplier relationships. A characterizing feature of PBC is tying the supplier's payment to performance–based metrics. A notable example is Roll Royce's Power–by–the–hour model whereby compensation for aircraft maintenance services is tied to engine availability (hours flown). Selviaridis and Wynstra (2015) provide a comprehensive overview of the PBC literature spanning various disciplines. PBC is gaining increasing traction in the healthcare sector. Operations management literature has evaluated various reimbursement schemes designed to induce desired performance. Examples include Zhang et al. (2016) and

Andritsos and Tang (2018) who examine pay–for–performance (P4P) reimbursement schemes such as the Hospital Readmission Reduction Program in the U.S. under which hospitals are penalized for excess readmissions, Adida and Bravo (2019) who analyze business–to–business P4P contracts for healthcare referral services and Jiang et al. (2012) who examine PBC to account for access to care in outpatient services.

Pharmaceutical research and development and clinical trial design

Operations management literature has also addressed stakeholder interactions in pharmaceutical research and development. For example, partnerships between small biotechnology firms and pharmaceutical companies are vital for healthcare innovation and R&D. Usually, small biotechnology firms are financially constrained and seek out partnerships with large pharmaceutical companies to gain access to funding, capacity, and capabilities. Literature has explored the relationships between a biotechnology firm (innovator), typically responsible for the R&D of a drug, and a pharmaceutical company (marketer) engaged with the marketing and sales of a drug post–approval. Savva and Scholtes (2014) analyze and compare three contractual arrangements in this setting: co–development, licensing, and co–development with opt–out options. Bhattacharya et al. (2015) study pharmaceutical R&D contractual arrangements burdened by various agency issues. Crama et al. (2017) analyze the role of options as well as control rights in R&D collaborations. Xiao and Xu (2012) utilize a stylized model of an R&D alliance to explore royalty contract revision, while Taneri and De Meyer (2017) empirically study the choice of alliance structure in biopharmaceutical alliances. Researchers have extensively studied relationships between biotechnology firms and pharmaceutical companies in pharmaceutical R&D. Operations management scholars have also looked at relationships between pharmaceutical firms. For instance, Tian et al. (2021a) analytically study the conditions under which two pharmaceutical firms should collaborate rather than compete in the development of new drugs. It is worth noting that our research broadly relates to the considerable operations management literature that aims to improve the efficiency of trials through clinical trial design. To name a few, several recent works explore optimal patient recruitment to address trial timeline delays (Kouvelis et al. 2017, Tian et al. 2021b), utilization of surrogate outcomes to improve clinical trial design–

making and to speed up trials (Anderer et al. 2021), and flexible trial approval policies that account for trial duration and likelihood of completion (Bravo et al. 2021).

1.3 Summary of the Results and Contributions

Chapters 2 through 5 were written as standalone papers and can be read as such. All four chapters relate to and address one or more of the central themes discussed in the preceding subsection. Together, they from a unified dissertation on managing healthcare ecosystems.

In Chapter 2, to advocate for further involvement of supply chain management scholars in the healthcare domain, we categorize healthcare supply chains into four main categories. We then outline the key challenges, risks, and existing research for the supply chain. By detailing effective and efficient supply chain strategies that have been employed in practice, we also demonstrate the research potential of supply chain management to healthcare operations researchers. With this aim, we discuss our expectations of the major future developments in healthcare supply chains and potential research avenues.

In Chapter 3, we incorporate and build on the categorization and learnings from Chapter 2 and examine how supply chain thinking can be used in healthcare. We put forward a framework that aims to address the main challenges prevalent in healthcare services through a supply chain perspective. We contribute to the literature by offering readers a way to systematically think about how supply chain strategies and concepts can be applied and tailored to healthcare to achieve outcomes such as improving the quality of care and patient experience, while decreasing costs.

In Chapter 4, we characterize the conditions under which a pharmaceutical company should pursue a strategic partnership with a contract research organization rather than engage in a transactional arrangement and detail the way these relationships unfold. To the best of our knowledge, the relationships between contract research organizations and pharmaceutical firms have not been explored before. Thus, our research makes an important first step into analyzing research and development contractual relationships between pharmaceutical sponsors and their outsourcing partners. By examining a simple performance–based contract to govern relationships, we embark

on studying the effectiveness of PBC in the industry and assess whether such contracts can affect clinical trial duration. In doing so, our research adds to the growing operations management literature on PBC in healthcare. Alongside contractual incentives, we investigate what the client can actually do to assist its contractor in managing duration. We contribute to the co–production literature by evaluating the role of client transparency and commitment.

In Chapter 5, we examine the impact of clinical trial decentralization adoption by pharmaceutical companies, clinical trials sites and patients. Our focus lies on how decentralization alters the current clinical development landscape. We propose a conceptual framework that employs systems thinking to evaluate the impact on key stakeholders through an assessment of pain points. The framework provides decision makers and practitioners a systematic and reiterative way to identify pain points and assess possible solutions through the implementation of decentralized elements. We contribute to the literature on systems thinking and clinical trial design by offering a methodical way of uncovering and alleviating obstacles arising from the adoption of new operational models (e.g., trial decentralization).

References

Adida, E., F. Bravo. 2019. Contracts for healthcare referral services: Coordination via outcome–based penalty contracts. *Management Science* 65(3):1322–1341.

Anderer, A., H. Bastani, J. Silberholz. 2021. Adaptive clinical trial designs with surrogates: When should we bother? *Management Science* 68(3):1962–2002.

Andritsos, D.A., C.S. Tang. 2018. Incentive programs for reducing readmissions when patient care is co–produced. *Production and Operations Management* 27(6):999–1020.

Arnold, R.D., J.P. Wade. 2015. A definition of systems thinking: A systems approach. *Procedia Computer Science* 44:669–678.

Bayiz, M., C.J. Corbett. 2005. Coordination and incentive contracts in project management under asymmetric information. Working Paper Anderson Graduate School of Management, University of California, Los Angeles.

Behl, D.V., S. Ferreira. 2014. Systems thinking: An analysis of key factors and relationships. Procedia Computer Science 36:104–109.

Berwick, D.M., T.W. Nolan, J. Whittington. 2008. The triple aim: Care, health, and cost. *Health Affairs* 27(3):759–769.

Bestsennyy, O., G. Gilbert, A. Harris, J. Rost. 2021. Telehealth: A quarter–trillion–dollar post–COVID–19 reality? *McKinsey & Company*. Available at: https://www.mckinsey.com/industries/healthcare–systems–and–services/our–insights/telehealth–a–quarter–trillion–dollar–post–covid–19–reality. Accessed October 6, 2022.

Bhattacharya, S., V. Gaba, S. Hasija. 2015. A comparison of milestone–based and buyout options contracts for coordinating R&D partnership. *Management Science* 61(5):963–978.

Bravo, F., T.C. Corcoran, E.F. Long. 2022. Flexible drug approval policies. *Manufacturing & Service Operations Management* 24(1):542–560.

Charlesworth, A., P. Johnson. 2018 *Securing the future: Funding health and social care to the 2030s.* London: Institute for Fiscal Studies, Health Foundation.

Chen, S., H. Lee. 2017. Incentive alignment and coordination of project supply chains. *Management Science* 63(4):1011–1025.

Chen, T., T. Klastorin, M.R. Wagner. 2015. Incentive contracts in serial stochastic projects. *Manufacturing & Service Operations Management* 17(3):290–30.1

Christopher, M.L. 2016. *Logistics and supply chain management*, 5th ed. (Pearson Education, Harlow, UK).

Congressional Budget Office. 2021. Research and development in the pharmaceutical industry. *Congressional Budget Office Report*. Available at: https://www.cbo.gov/publication/57126. Accessed January 5, 2023.

Crama, P., B. De Reyck, N. Taneri. 2017. Licensing contracts: Control rights, options, and timing. *Management Science* 63(4):1131–1149.

Dawande, M., G. Janakiraman, A. Qi. 2019. Optimal incentive contracts in project management. *Production and Operations Management* 28(6):1431–1445.

de Vries, J., R. Huijsman. 2011. Supply chain management in health services: An overview. *Supply Chain Management* 16(3):159–165.

Feng, T., Z.J. Ren, F. Zhang. 2019. Service outsourcing: Capacity, quality and correlated costs. *Production and Operations Management* 28(3):682–669.

GlobeNewswire. 2021. Rising protocol design complexity is driving rapid growth in clinical trial data volume, according to the Tufts Center for the Study of Drug Development. Available at: https://www.globenewswire.com/en/news–release/2021/01/12/2157143/0/en/Rising–Protocol–Design–Complexity–Is–Driving–Rapid–Growth–in–Clinical–Trial–Data–Volume–According–to–Tufts–Center–for–the–Study–of–Drug–Development.html. Accessed January 17, 2023.

Grand View Research. 2022. Digital health market size & share report. Available at: https://www.grandviewresearch.com/industry–analysis/digital–health–market. Accessed October 6, 2022.

Hajat, C., E. Stein. 2018. The global burden of multiple chronic conditions: A narrative review. *Preventive Medicine Reports* 12:284–293.

Jiang, H., Z. Pang, S. Savin. 2012. Performance–based contracts for outpatient medical services. *Manufacturing & Operations Management* 14(4):654–669.

Kim, S.–H., I.–W.G. Kwon. 2015. The study of healthcare supply chain management in United States: Literature review. *Management Review: An International Journal* 10(2):34–56.

Kouvelis, P., J. Milner, Z. Tian. 2017. Clinical trials for new drug development: Optimal investment and application. *Manufacturing & Service Operations Management* 19(3):437–452.

Kurani, N., J. Ortaliza, E. Wager, L. Fox, K. Amin. 2022. How has U.S. spending on healthcare changed over time? *The Peterson Center on Healthcare and Kaiser Family Foundation.* Available at: https://www.healthsystemtracker.org/chart–collection/u–s–spending–healthcare–changed–time/#Total%20national%20health%20expenditures,%20US%20$%20Billions,%201970–2020. Accessed January 5, 2023.

Kwon, H.D., S.A. Lippman, K.F. McCardle, C.S. Tang. 2010a. Project management contracts with delayed payments. *Manufacturing & Service Operations Management* 12(4):692–707.

Kwon, H.D., S.A. Lippman, C.S. Tang. 2010b. Optimal time–based and cost–based coordinated project contracts with unobservable work rates. *International Journal of Production Economics* 126(2):247–254.

Meadows, D.H. 2008. Thinking in systems: A primer. White River Junction, VT: Chelsea Green Publishing. Pg. 11.

Mentzer, J., W. DeWitt, J. Keebler, S. Min, N.W. Nix, C.D. Smith, Z. Zacharia. 2001. Defining supply chain management. *Journal of Supply Chain Management* 22(2):1–25.

Merriam–Webster. 2022. System. Available at: https://www.merriam–webster.com/dictionary/system. Accessed October 30, 2022.

Monat, J.P., T.F. Gannon. 2015. What is systems thinking? A review of selected literature plus recommendations. *American Journal of Systems Science* 4(1):11–26.

National Collaboration for Integrated Care and Support. 2013. *Integrated care and support: Our shared commitment.* May 2013. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/198748/DEFINITIVE_FINAL_VERSION_Integrated_Care_and_Support_–_Our_Shared_Commitment_2013–05–13.pdf.

Passut, C. 2020. Trend of longer trial timelines is likely to continue. *CenterWatch.* Available at: https://www.centerwatch.com/articles/25033–trend–of–longer–trial–timelines–is–likely–to–continue. Accessed January 17, 2023.

Raghupathi, W., V. Raghupathi. 2018. An empirical study of chronic diseases in the United States: A visual analytics approach. *International Journal of Environmental Research and Public Health* 15(3):431.

Rahmani, M., G. Roels, U.S. Karmarkar. 2017. Collaborative work dynamics in projects with co–production. *Production and Operations Management* 26(4):686–703.

Royal Academy of Engineering, Royal College of Physicians and The Academy of Medical Sciences. 2017. Engineering better care: A systems approach to health and care design and continuous improvement. Available at: https://raeng.org.uk/media/wwko2fs4/final–report–engineering–better–care–version–for–website.pdf. Accessed October 30, 2022.

Savva, N., S. Scholtes. 2014. Opt–out options in new product co–development partnerships. *Production and Operations Management* 23(8):1370–1386.

Selviaridis, K., F. Wynstra. 2015. Performance–based contracting: a literature review and future research directions. *International Journal of Production Research* 53(12):3505–3540.

Sommer, C., D. Zuccolin, V. Arnera et al. 2018. Building clinical trials around patients: Evaluation and comparison of decentralized and conventional site models in patients with low back pain. *Contemporary Clinical Trials Communications* 11:120–126.

Song, J.M., Y. Zhao, X. Xu. 2021. Incentives and gaming in collaborative projects under risk–sharing partnerships. *Manufacturing & Service Operations Management* 23(2):453–470.

Sterman, J.D. 2000. Business dynamics: Systems thinking and modeling for a complex world. New York: McGraw–Hill.

Taneri, N., A. De Meyer. 2017. Contract theory: Impact on biopharmaceutical alliance structure and performance. *Manufacturing & Service Operations Management* 19(3):453–471.

Tian, Z., H. Gurnani, Y. Xu. 2021. Collaboration in development of new drugs. *Production and Operations Management* 30(11):3943–3966.

Tian, Z., W. Han, W.B. Powell. 2022. Adaptive learning of drug quality and optimization of patient recruitment for clinical trials with dropouts. *Manufacturing & Service Operations Management* 24(1):580–599.

Vairaktarakis, G.L. 2013. Noncooperative games for subcontracting operations. *Manufacturing & Service Operations Management* 15(1):148–158.

Van Norman, G.A. 2021. Decentralized clinical trials: The future of medical product development? *JACC: Basic to Translational Science* 6(4):384–387.

WHO. 2023. Health workforce. Available at: https://www.who.int/health–topics/health–sworkforce#tab=tab_1. Accessed January 5, 2023.

Williams, E. D. Buck, G. Babalola, D. Maguire. 2022. What are health inequalities? *The King's Fund.* Available at: https://www.kingsfund.org.uk/publications/what–are–health–inequalities. Accessed January 5, 2023.

Xiao, W., Y. Xu. 2012. The impact of royalty contract revision in a multistage strategic R&D alliance. *Management Science* 58(12):2251–2271.

Zhang, H., G. Kong, S. Rajagopalan. 2018. Contract design by service providers with private effort. *Management Science* 64(6):2672–2689.

Zhang, D.J., I. Gurvich, J.A. Van Mieghem, E. Park, R.S. Young, M.V. Williams. 2016. Hospital readmissions reduction program: An economic and operational analysis. *Management Science* 62(11):3351–3371.

Chapter 2

Healthcare Supply Chains

2.1 Introduction

Historically, healthcare supply chains have commonly been associated with the procurement and logistics of healthcare supplies and services. However, recent developments in healthcare render this understanding too narrow. This chapter broadens the definition of supply chains in healthcare ecosystems by using concepts from traditional supply chains and supply chain management. The chapter groups healthcare supply chains into four main categories: health services, pharmaceutical, special health services, and health humanitarian supply chains. Next, the chapter discusses the key strategies, challenges, and risks as well as the existing research for these categories. The chapter concludes with a short discussion on future research.

Christopher (2016) defines a supply chain (SC) as a "network of organizations that are involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services in the hands of the ultimate consumer" (13). The author defines supply chain management (SCM) as the "management of upstream and downstream relationships with suppliers and customers in order to deliver superior customer value at less cost to the supply chain as a whole" (3). It is clear from these definitions that every SC is a system of organizations, materials, resources (including human capital), activities, information, and finances that help move a product or service from suppliers to end customers/consumers while optimizing end–to–end efficiency and effectiveness. As a result, to match customer requirements with supply constraints, SCM as a management strategy is characterized by a *systems approach* (i.e., considers the organizations in the SC as an end–to–end, integrated entity), a *strategic orientation* (i.e., aligns the intra– and interfirm goals and capabilities with those of the SC), and a *customer focus* (i.e., focuses on customer value as the key driver of the SC's activities) (Mentzer et al. 2001). This

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definition of SCM can easily be extended to healthcare supply chains (hSCs). Healthcare supply chain management is the management of people (such as patients, providers, purchasers, and payers), processes, information, and finances to deliver medical products (pharmaceuticals, medical devices, and health aids) and services (curative, preventive, rehabilitative, and palliative care) to consumers and to enable the flow of patients in the care system, all in the pursuit of enhancing clinical outcomes and user experience, while controlling costs (de Vries and Huijsman 2011).

In recent years, the world's population has been increasing and aging. Consequently, countries are spending a significant portion of their gross domestic product on healthcare. There are well–documented inefficiencies in healthcare delivery, leading to wastes. Therefore, the need to contain costs while ensuring quality care is evident. Improved SCM lends itself as an opportunity to deliver effective and affordable healthcare.

The remainder of the chapter is organized as follows. We group hSCs into four main categories: health services, pharmaceuticals, special health services, and health humanitarian supply chains. Because of space considerations, we refer the reader to Oloruntoba and Gray (2006), Ertem, Buyurgan, and Rossetti (2010), and Wagner and Thakur–Weigold (2018) for a discussion on humanitarian supply chains and to Parvin et al. (2018) for an application in healthcare. We discuss the key strategies, challenges, and risks as well as the existing research for the remaining categories. For each hSC, we provide at least one efficient and effective SC strategy that has been used in practice. We close each section with a short discussion on future research. The chapter ends with several concluding remarks. Two caveats are worth mentioning. Because of our familiarity with the healthcare systems in the United States and the United Kingdom, our descriptions of hSCs are predominantly based on the context of these two countries. Also, there exists a large body of operations management literature in the realm of healthcare. For the sake of brevity, we discuss only a few academic papers for each supply chain.

Health Services Supply Chains

We subcategorize health services SCs into medical, community and social care, workforce, reimbursement, and supplies and equipment supply chains.

2.2 Medical Supply Chains

Medical care provision takes place across primary, secondary, and tertiary care. Primary care refers to the first healthcare point of contact for patients (e.g., general practitioners [GPs], pharmacists). Secondary care encompasses hospital, clinic, or community care (e.g., planned operations, emergency care), while tertiary care refers to highly specialized treatment (e.g., neurosurgery). Patients flow across primary, secondary, and tertiary care in several ways. We note that patient flows can refer to either patient "pathways" or patient "journeys" and it is important to distinguish between the two. Patient or clinical pathways are standardized plans of care for patients with a particular diagnosis. Patient journeys refer to how patients proceed through healthcare systems; Trebble et al. (2010) outline how to employ process mapping to capture and examine a patient journey.

At a high level, a typical patient flow begins with patients first visiting their GPs. Aside from GPs, other primary care providers include pharmacies, optometry, and dental services. After consulting with a primary care provider, patients can subsequently be referred to a hospital. Patients visiting hospital outpatient clinics do not require a bed and thus differ from inpatients who are admitted to a hospital. Patients who have a prearranged date to stay in a hospital are considered elective admissions. Alternatively, patients can also present to a hospital's emergency department (ED), via ambulance or walk–in, as nonelective patients. After being seen by a healthcare provider, ED patients are either discharged (to go home, to community care, etc.) or admitted to the hospital. Inpatients may require surgery in operating rooms, need to stay in intensive care units, or need further treatment and rehabilitation in various wards.

Figure 2.1 depicts a broad and simplified version of typical patient flow for a patient episode, which is typically initiated by a referral or admission and is ended by a discharge. Several remarks are in order for Figure 2.1. First, within the hospital, different patients visit different departments, and within one admission stay, a patient may switch between wards multiple times. Second, one can identify various flows *within* each department. For example, when a patient visits the ED, they are first triaged by medical staff (often a nurse). The patient may then undergo medical tests, receive physician consultations, and be administered medications and treatments. Finally, the patient is discharged or admitted. Third, patients can be transferred from one hospital to another.

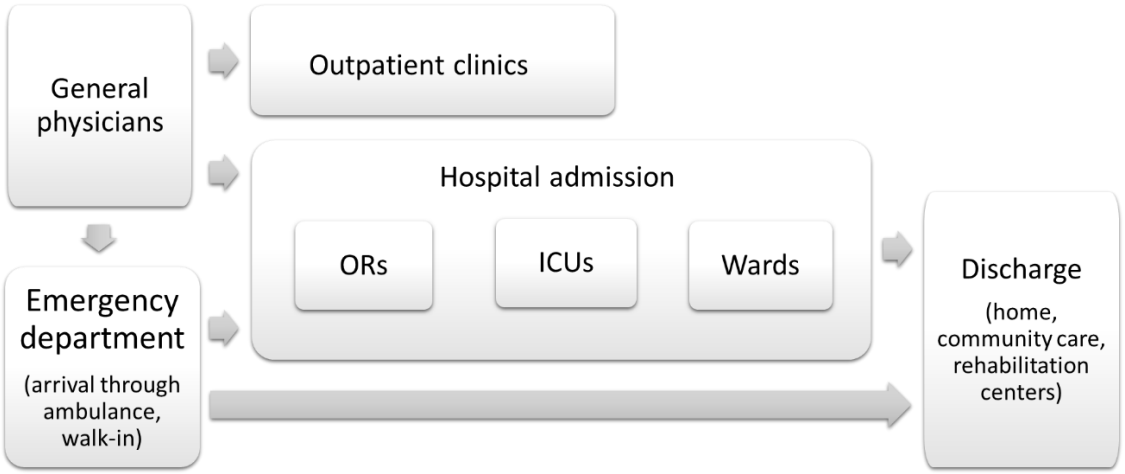

Figure 2.1 A simplified and broad overview of the medical supply chain.

Unlike traditional SCs, patients rather than materials or products flow through different stages of this hSC, within and across care facilities. Therefore, a critically important task is to accurately move patients between stages in a timely and efficient manner. Otherwise, patient safety, health outcomes, and experience can become compromised, and resources may be wasted. System coordination plays a vital role in hospital operations. Bretthauer et al. (2011) show that one of the key reasons for poor performance at EDs is bed blocking (in which patients who need to be admitted occupy limited ED beds as a result of bed unavailability in wards). A further instance of bed blocking, or delayed transfer of care, occurs when (mainly elderly) patients stay in the hospital for excessive periods because of a lack of space in community care. Another difficult task is patient routing within hospitals. In some cases, patients are routed to nonpreferred wards because of bed shortages in preferred wards. These outlier patients may need to be transferred to appropriate wards

later. Stylianou, Fackrell, and Vasilakis (2017) report that 10 percent of admitted patients are outliers. Delayed transfer of care and outlier transfers may result in patients receiving delayed treatment and an increase in patients' length of stay, which also has economic ramifications. Freeman, Robinson, and Scholtes (2018) show that quality of care is improved if departmental routing is consistent, that is, if the same types of patients are served in the same department, and that consistent referral is particularly beneficial for the most complex patients (emergency patients with multiple comorbidities).

Lu and Lu (2018) empirically study the interhospital patient routing decisions in the case of patients suffering from acute myocardial infarction. The authors uncover the determinants of transfer destinations and show that the hospital relationship (when the two hospitals are affiliated with the same hospital system) plays a larger role than the distance between the two hospitals and the quality of the receiving hospital, which has negative implications on readmission rates. Wang et al. (2018) examine how scheduling can be improved between two service providers involved in preoperative care who often reside in separate clinics. The authors propose a coordinated scheduling policy that takes into account system profit from both services, patient waiting time, and clinic overtime. These results have strong implications, especially in the face of policy initiatives to reduce readmission rates and waiting time. Inefficiencies such as delayed transfer of care and patient outliers illustrate that patient SCs are prone to fragmentation. Care fragmentation threatens health outcomes, patient experience, and continuity of care. To overcome the lack of coordination between providers and ensure timely and appropriate patient flow, new care models such as integrated care initiatives are receiving growing attention. We refer the reader to NHS Improvement (2017) for a series of case studies describing various initiatives UK trusts have undertaken to improve patient flow. Researchers should, therefore, direct their efforts in analyzing what these models mean for system capacity, scheduling, and patient routing decisions from an SCM perspective. There is a wealth of operations management literature regarding scheduling carrying implications for individual hospitals. Expanding this research in a multihospital context or across stakeholders (e.g., capacity management between hospitals and nursing homes) has the potential to simultaneously build on hSC research and address fragmentation in healthcare.

2.3 Community and Social Care Supply Chains

The provision of community care occurs in residential settings (such as patient's homes, community centers, and schools). Community care captures a diverse set of services ranging from adult care (e.g., district nursing and palliative care), therapy services (e.g., physiotherapy, occupational therapy, and speech and language therapy), preventative services (e.g., sexual health and smoking cessation clinics), and health promotion services (e.g., school nursing and health visiting) to specialist services such as offender healthcare (Charles 2019). In England, community care accounts for one pound in every ten pounds spent by healthcare commissioners, with district nursing, health visiting, and midwifery care accounting for the largest cost, and providers include the National Health Service (NHS), general practice, private providers, local authorities, charities, social enterprises, and community interest companies (Gershlick and Firth 2017). Community care services offer care and support for patients with long–term conditions and complex health needs and play a role in assisting individuals to live independently in their homes. Community care workers coordinate care with other health services (such as GPs and hospitals) and social care providers. With an increase in the prevalence of chronic diseases, demand for community care is likely to rise. However, a growing shortage in key parts of the workforce will make it difficult to meet demand. For instance, between 2010 and 2018 the total number of NHS nurses working in community health services fell by 14 percent while the number working in acute adult health increased by 9 percent (Charles 2019). Reinforcing community–based care is particularly important, especially in the face of a growing focus to bring care closer to patients' homes as well as to relieve pressure from other parts of the healthcare system (NHS England 2013).

Social care is the provision of care and support to individuals requiring assistance in daily activities such as cooking, cleaning, and personal hygiene. These needs arise as a result of age, illness, physical disability, or mental health. The number of people aged 65 and over is growing three times faster than the number of people under 65 (Charlesworth and Johnson 2018). There is also a rising burden of disease as more individuals are living with a chronic disease and many are affected by more than one condition. The report also highlights an increasing trend of younger adults who live with a disability. As life expectancy increases, the cost of care for disabled persons is rising.

Social care for people of working age is now costing public bodies about as much as that for older people (NHS Digital 2017, Bottery et al. 2018).

A representative social care SC based on the UK system is shown in Figure 2.2. In England, local authorities are responsible for public funds directed to social care services and the commissioning of care. Eligibility depends on both needs and financial means assessment (Bottery et al. 2018). Unlike public spending on health, expenditure on social care has been falling since 2009–10 (Charlesworth and Johnson 2018). Currently, a large portion of care is privately paid for, with no cap on the amount that individuals must pay out of pocket (King's Fund 2018).

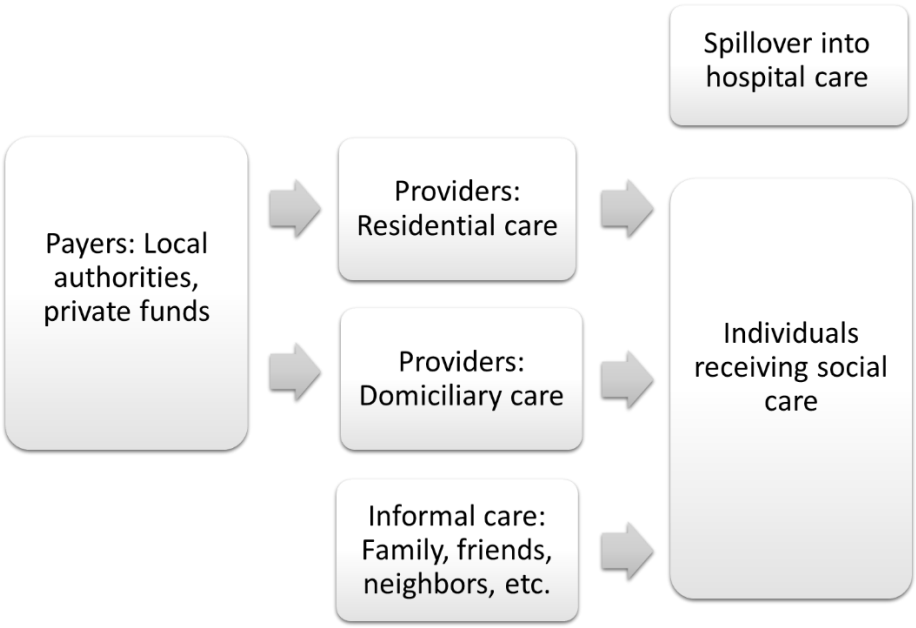

Figure 2.2 A representative social care supply chain in the UK context.

Providers of social care consist of private, for–profit, or nonprofit entities, providing residential care or domiciliary care (i.e., care at individuals' homes). These organizations include residential care homes, nursing homes, and specialist colleges providing personal care and accommodation (King's Fund 2018). Perhaps surprisingly, the workforce involved in social care is larger than that of the NHS (Charlesworth and Johnson 2018). The sector faces high turnover rates, and it is projected that there will be an increased need for staff to meet the rising demand for social care (Bottery et al. 2018; King's Fund 2018). Relatives, friends, and neighbors also provide a large

portion of care, termed informal care. This often results in carers having to partially, or entirely, leave the labor force.

There has been a decrease in publicly accessed social care in the United Kingdom since 2009 and it is speculated that this has put a greater strain on informal care (Charlesworth and Johnson 2018). Additionally, individuals with unmet social needs may be ending up in hospitals or relying more heavily on GPs. A portion of delayed transfer of care can be attributed to social care because awaiting a home care package is still the number one reason for delayed hospital discharge (Bottery et al. 2018). Another key challenge brought about by public budget cuts is that it has become more expensive for individuals who privately pay for services as providers have engaged in cross–subsidization between rates charged to publicly and privately funded individuals (Charlesworth and Johnson 2018).

Technology has changed and continues to change the way healthcare and social care organizations operate. Lu, Rui, and Seidmann (2018) empirically investigate the effect of information technology adoption on staffing and resident admissions in US nursing homes. In this industry, there is high competition across providers, payment is both private and public, and quality is mainly determined by nurse staffing policies. On the one hand, the authors show that automation leads to an increase in staffing levels in low–end nursing homes because it makes care providers more productive (a complementary effect). On the other hand, nurse staffing levels decrease after automation in high–end homes. This is because technology may serve as a substitute for labor since the marginal benefit of providing additional quality (in a high–end nursing home) is relatively low. Notably, it is shown that increased automation decreases admissions of less profitable residents (those paid for by Medicaid).

As the population grows and ages, there is an increasing demand for social care as well as healthcare. Care models that integrate social and healthcare provision play a key role in ensuring patient centricity and the holistic management of patient needs (National Collaboration for Integrated Care and Support 2013). Thus, future research should examine the interaction between the two sectors. There has also been a push toward bringing care as close to patients' homes as possible. A 2013 report by the NHS England outlines the elements required to transform urgent

and emergency care services in England and bring care closer to patients' homes (NHS England 2013). The report highlights the fact that improving technologies allow for the management of many problems in a patients' home or local community that would have required hospital admission in previous years. The report also advocates for the support and promotion of self–care by the NHS. Individuals, especially those with long–term conditions, can become experts in their problems. With the proper information and advice (e.g., through accessible and reliable telephone services), patients can become capable of managing many problems themselves or with the help of friends and family. Shifting care from hospitals to patients' homes has the potential to improve the quality of care (e.g., eliminate the risk of hospital infections), patient experience, and comfort, as well as reduce costs. The Buurtzorg model of care or *neighborhood care* emerged and operates in the Netherlands. Under this model, nurse teams are responsible for a few dozen patients in a particular area. Nurses act as health coaches for patients and their families by offering advice and advocating preventative care. In addition, nurses also provide some care themselves or elicit the services of other providers (Brindle 2017). A brief by the Royal College of Nursing discusses the success of this community care program as well as how it may be adapted to a UK context (Royal College of Nursing 2016).

2.4 Workforce Supply Chains

Healthcare staff such as doctors, nurses, and therapists are arguably the single most important asset to hSCs. Jointly with social care, jobs in the healthcare sector account for over 10 percent of total employment in many countries belonging to the Organisation for Economic Co–operation and Development (Organisation for Economic Co–operation and Development 2016). The NHS employs over a million people. However, it has been reported that there is a current shortfall of one hundred thousand staff, and this may take a toll on waiting lists, patient care, and staff experience (Beech et al. 2019). This also seems to be the case for social care, with one in ten social workers' roles vacant (Health Foundation 2018). Beech et al. (2019) warn that there should be collaborative workforce planning between the two sectors, because the NHS can have significant "gravitational pull" on social care staff.

The supply of clinical workforce depends on the inflow of trained doctors and nurses. The inflow depends on annual quotas for the admission of medical students, postgraduate training places for general medicine, and reliance on foreign–trained workers. Retention of professionals is another important criterion. For example, policies regarding pension and retirement age as well as measures enacted to reduce student attrition (e.g., through funding) and retain professionals (by changing working conditions) can alter the outflow of healthcare workers.

The workforce has been changing and new healthcare roles have emerged as part of innovative workforce management. Physician associates (PAs), medically trained generalists who work under the supervision of doctors, have patient lists, and perform diagnostic and therapeutic procedures. However, they have a limited scope of practice (e.g., they are unable to prescribe or request x–rays or computed tomography scans) (NHS England 2019). The role appeared in the United States fifty years ago and in the early twenty–first century 100,000 PAs work in both primary and secondary care in the country. In comparison, there are 350 practicing Pas and another 550 in training in the NHS (NHS England 2019). A study conducted by the National Institute for Health Research has demonstrated the impact of PAs in hospitals (National Institute for Health Research 2019). The PAs support the workloads of clinical teams and contribute to team continuity (e.g., by inducting new junior doctors). This allows doctors to tend to more complex patients and attend training. In addition, PAs were found to positively impact patient flow and experience. To ensure patient continuity of care and to alleviate the GP shortage in primary care, the Department of Health and Health Education England has expressed an interest in the recruitment of more PAs into primary care (NHS England 2019).

Not only are roles arising, but also traditional job boundaries are gradually blurring as workers perform more and more tasks formerly executed solely by professionals higher up in the healthcare hierarchy (Oxtoby 2009). According to Oxtoby (2009), “pharmacists are screening, nurses are prescribing, GPs are specializing, and consultants are increasingly taking on managerial roles.” Blouin and Adams (2017) discuss the role pharmacists play in healthcare *delivery* (in assuring appropriate medication therapy management), healthcare *access* (by providing a variety of services as one of the most accessible health professionals), and *public health* (such as facilitating

appropriate prescription opioid use, providing increased access to immunizations, and contributing to disaster response by administering medication, education, and care for individuals).

Taken together, it is clear that the dynamics (e.g., the types and number of workers) of the workforce inflow are evolving. Policy makers can also influence the geographic distribution of medical workers. In certain countries like Canada, there is a significant shortage of doctors in rural areas. The Organisation for Economic Co–operation and Development (2016) outlines various ways in which this may be addressed, including financial incentives, the use of telemedicine, regulations (e.g., restrictions to set up practice in adequately supplied areas), and competency transfer from doctors to nurses. It is also important to note that nonclinical staff (such as receptionists, accountants, and information technology specialists) also constitute a portion of the healthcare workforce.

The management of the inflow and outflow of healthcare workers underlies SCM of the healthcare workforce. Currently, there is a severe shortage of human resources in healthcare, with an estimated 17.4 million healthcare workers missing from the global medical sector (Medical Futurist 2018), which has put pressure on healthcare personnel to do more with less. We caution that SC improvements should focus on system–wide changes rather than simply increasing expectations from the workforce. The human resource crisis may lead to opportunities for process optimization in healthcare. In addition, as in many other sectors, technological advancements are influencing the healthcare workforce. Technologies such as artificial intelligence and telemedicine may help ease the burden on healthcare providers. For instance, artificial intelligence may facilitate more accurate diagnosis, assist in decision–making, and execute repetitive or bureaucratic tasks so that clinicians can concentrate their efforts on value–adding activities (Medical Futurist 2018). Although wider adoption of health technologies has the potential to ameliorate the human resource shortage, many questions arise regarding the ethics, implementation, and feasibility of applying various technological advancements in healthcare delivery. Further exploration is required concerning the opportunities and challenges of new technologies to health providers.

2.5 Reimbursement Supply Chains

Financing is an important part of healthcare services, and the reimbursement of healthcare providers has been, and continues to be, a subject of debate and research interest. Different countries have different reimbursement systems. Some countries, like England, have a universal healthcare system in which residents have free access to healthcare, which is paid for by government general taxation. In the United States, Medicare and Medicaid are federal and state programs that offer coverage to elderly and low–income individuals, respectively. The remaining population is either privately insured or uninsured. Many countries employ hybrid systems in which payers may be central and local governments, insurance companies, employers, charity organizations, relatives, and patients themselves. Patients receive healthcare services from providers (such as hospitals, clinics, and physicians), who are accordingly reimbursed by payers. Many different reimbursement schemes have been evaluated in the literature. These schemes range from block contracts and fee–for–service payments, which have been used in the past, to recently introduced diagnosis–related group–based and/or performance–based prospective payment schemes based on bundles, outcomes, and values. Jiang, Pang, and Savin (2012) review some of these popular contracts. It is worthwhile to note that capitation has recently regained attention because this payment scheme facilitates the reimbursement of integrated care (e.g., accountable care organizations) without the use of complicated and segmented contracts.

Adida and Bravo (2019) explore the issue of coordinating referral services in a business–to–business context in which managing organizations (requesters, who are financially responsible for the care patients receive) refer patients to third–party providers when advanced care is needed. Both requesters and providers can exert effort to decrease further costly interventions. The authors show that social welfare can be improved under a penalty contract relative to a fee–for–service contract. Calsyn and Lee (2012) discuss alternatives to fee–for–service payments in healthcare and present several case studies outlining recent reform projects in the United States. For example, in 2002, the Centers for Medicare and Medicaid Services implemented the hospital readmissions reduction program, which lowers payments to hospitals with excess thirty–day readmissions. The program supports the national goal of improving healthcare for Americans by linking payments to the quality of hospital care (Joynt et al. 2016).

As new care models become increasingly focused on system coordination and integration, reimbursement is fundamental in ensuring cooperative behavior. Furthermore, there is a need to ensure the seamless transition of reimbursement schemes theoretically proposed in the literature into practice.

2.6 Supplies and Equipment Supply Chains

This SC focuses on the procurement, logistics, and inventory management of supplies and the purchase, operation, maintenance, and repair of medical equipment. We refer the reader to de Vries and Huijsman (2011) and Kim and Kwon (2015) for reviews on the management of healthcare supplies and provide a short discussion on equipment SCs.

The sophistication and cost of medical equipment, and consequently its maintenance, continue to escalate. An equipment breakdown can have substantial consequences such as risk of injury or death to the user or the patient, inappropriate therapy, or misdiagnosis (World Health Organization 2011). Therefore, equipment must be properly maintained to ensure its safety and reliability. In addition, equipment failures impact equipment availability, which, in turn, can adversely affect care quality, patient wait times (Cruz and Rincon 2012), and hospital financials. Maintenance and repair of medical equipment require financial, physical (e.g., testing and calibration tools), and human resources. Maintenance services can be preventative (which seek to reduce the failure rate of equipment) or corrective (which restore the function of equipment that has already failed) and various services can be executed in house, by the original equipment manufacturer or a third–party provider (World Health Organization 2011).

With an external maintenance provider, value is coproduced (Karmarkar and Roels 2015) because operational performance depends on both the operator handling of the equipment and the maintenance effort on the part of the provider. Recently, Chan, de Véricourt, and Besbes (2019) empirically examine the two contract types for the provision of maintenance services of medical imaging devices. Using sales and service data on 712 computed tomography and magnetic resonance imaging scans sold to 441 hospitals by a large original equipment manufacturer in a major Organisation for Economic Co–operation and Development country, the authors find that

moving from a basic pay–per–service plan to a fixed–fee, full protection plan reduces reliability (increases failure rate by 33 percent) and increases service costs. The authors caution against the prevailing view that providers should assume more equipment failure risk. It is suggested that this may lead to incentive effects that lower the operator's level of care. Chan, de Véricourt, and Besbes (2019) show that although both contract schemes are used in practice, a pay–per–service plan significantly improves operational performance metrics over a fixed–price full–protection plan.

The operational performance of medical equipment (e.g., the failure rate) is largely determined by the client's decisions, such as the training of operators (Jain, Hasija, and Popescu 2013). This is particularly evident in developing countries where the overarching reliance on external vendors for maintenance services (Cruz and Rincon 2012) and out–of–service equipment (Malkin and Whittle 2014) is attributed to the absence of properly trained staff. Malkin and Whittle (2014) examine a program offered by Engineering World Health that served to train biomedical technicians in Rwanda. The researchers demonstrate that nearly twice as much equipment was out of service at hospitals where technicians had not been trained compared to hospitals where technicians had completed one year of training. Operators may also lack the material resources to handle maintenance activities on their own. It has been reported that original equipment manufacturers deny other organizations access to documentation and products such as online diagnostics programs to create barriers to competition (Blumberg 2004). This suggests that more collaborative arrangements between manufacturers and operators as well as greater support offered by original equipment manufacturers have the potential to improve the operational performance of equipment. Thus, we encourage researchers to examine how more value can be achieved in medical equipment SCs in developing countries.

Pharmaceutical Supply Chains

We subcategorize pharmaceutical SCs into two: (1) innovation and research and development and (2) manufacturing and distribution supply chains[1].

[1] As suggested by Professor Stefan Scholtes, another way to subcategorize pharmaceutical SCs is into two separate categories: (1) the activities prior to the expiration of a pharmaceutical's market exclusivity period and (2) the activities following the expiration of market exclusivity. This is due to the fact that the innovation, research and development as well as the marketing processes for branded drugs are very different than those of generic drugs.

2.7 Innovation and Research and Development Supply Chains

Drug discovery and development is a long and costly process that can take on average, ten to fifteen years and cost $2.6 billion (PhRMA 2016). To gain regulatory (e.g., Food and Drug Administration in the United States) approval, potential medicines move through preclinical testing and several phases of clinical trials. Human testing commences at phase 0, where pharmacodynamics and pharmacokinetics (i.e., how a drug affects an organism and how an organism affects a drug, respectively) are determined. Drug safety is evaluated in phase 1, efficacy is assessed in phase 2, and both are confirmed in phase 3 on a large scale. Phase 4 studies or postmarketing surveillance studies are conducted after a drug has been approved. The sponsoring firm, typically a pharmaceutical company, along with collaborators involved in conducting trials, needs to engage multiple test sites (often in various locations) and recruit, treat, and test hundreds or even thousands of volunteers. A large portion of R&D expenditure goes toward clinical trials. DiMasi, Grabowski, and Hansen (2016) estimate the mean expenses for phases 1, 2, and 3 to be $25.3 million, $58.6 million, and $255.4 million, respectively. Costs of R&D have rapidly escalated since the 1970s (DiMasi, Grabowski, and Hansen 2016). This has been the result of larger and more complex trials, a greater focus on chronic diseases, and high failure rates for drugs (less than 12 percent of candidate medicines going into phase 1 are subsequently approved) (PhRMA 2016). To shorten development times and contain costs, pharmaceutical firms have undertaken a variety of measures such as mergers and acquisitions, downsizing in–house development efforts, and instead outsourcing R&D activities (Rafols et al. 2014). The outsourcing of clinical trials to contract research organizations has caused such organizations to flourish into a multi–billion–dollar industry (Betcheva and Erhun 2018). Other entities involved with the conduct of trials include academic institutions, hospitals, biotechnology companies, research institutes, government agencies, and nonprofits, among others.

The pharmaceutical R&D SC is better depicted by an ecosystem of various entities that provide different resources and capabilities (see Figure 2.3). For instance, academic institutions and biotechnology firms provide basic research, expertise, and technologies, while pharmaceutical firms offer funding and capacity for full–scale clinical development. Relationships between entities range from purely transactional to more integrated partnerships involving risk and revenue

sharing (such as joint ventures among large pharmaceutical companies). Partnerships between small biotechnology firms and pharmaceutical companies are vital for healthcare innovation; see Savva and Scholtes (2014) and Bhattacharya, Gaba, and Hasija (2015).

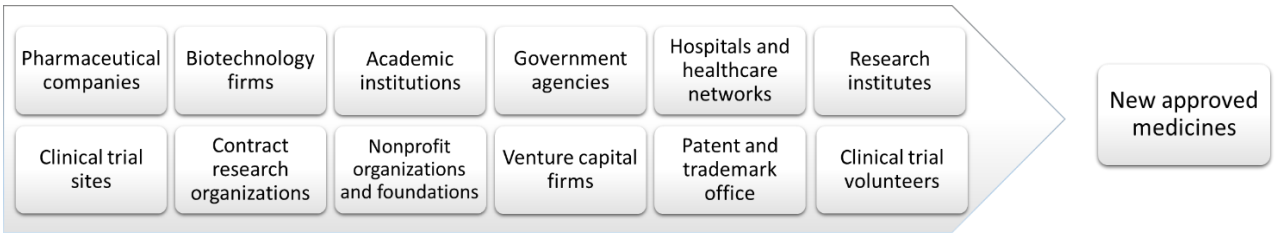

Figure 2.3 Pharmaceutical innovation and research and development supply chain.
Note: We refer the reader to PhRMA (2016) for a more comprehensive representation of this SC.

Motivated by the lack of operational decision support research in the context of clinical trials, Kouvelis, Milner, and Tian (2017) seek to provide insights as to how sponsoring firms or administering contract research organizations can determine when and how many test sites should be opened and the number of patients to enroll over time. The problem is modeled under a dynamic program that has the objective of maximizing the net present value of a drug. Trial costs, drug quality, interim analyses of clinical results, the likelihood of approval, and the expected commercial value after approval are considered in the formulation. The authors characterize the optimal policy as a series of thresholds on both decision variables.

Advancements in technology and artificial intelligence provide opportunities for personalization, efficiency, and alignment in pharmaceutical SCs. For example, Healx (a Cambridge–based tech venture) focuses on drug development for rare diseases in the emerging field of personalized medicine (Kavadias, Ladas, and Loch 2016). Rare diseases are often ignored by pharmaceutical companies because of their small market potential and expensive drug development process. To remedy this, guided by a pharmacology team, Healx uses its proprietary artificial intelligence–based tool (Healnet) to identify and repurpose existing drugs to treat rare diseases. Healx partners closely with patient groups to understand the clinical need and disease information. Quality curated data are then fed into Healnet to predict treatments, which are subsequently reviewed by expert

pharmacologists. This results in a faster and cheaper approach to developing treatments for rare diseases (Healx 2019).

2.8 Manufacturing and Distribution Supply Chains

Narayana, Pati, and Vrat (2014) present a systematic review of research on pharmaceutical SCM. The authors identify four key customer healthcare needs for pharmaceuticals—availability, access, affordability, and safety—and discuss how research has analyzed the final value delivered to customers through the SC. They go onto suggest that research has traditionally focused on efficiency improvements and that there is an emerging interest in process analysis and technology implementation. Figure 2.4 provides a simple depiction of a representative pharmaceutical manufacturing and distribution SC.

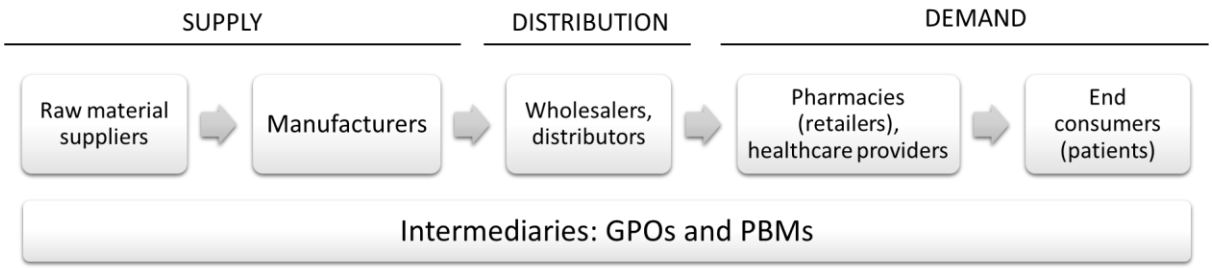

Figure 2.4 A representative pharmaceutical manufacturing and distribution supply chain.
Note: We refer the reader to Narayana, Pati, and Vrat (2014) for a more comprehensive representation of this supply chain.

Privett and Gonsalvez (2014) prioritize the top ten global pharmaceutical SC challenges. Shortage avoidance is among the ranked. Drug shortages are both costly (since alternative therapies must be sought) and lead to social welfare loss in terms of suboptimal patient outcomes. Jia and Zhao (2017) study how to minimize shortages for generic sterile injectable drugs, which possess particular characteristics rendering them vulnerable to shortfalls. These drugs have small profit margins, making them unattractive to manufacturers. Producers thus allocate low capacity toward

such drugs. Worse still, because of demanding storage environments, holding these drugs is costly. The authors model the hSC composed of a manufacturer, a group purchasing organization, the government, and a healthcare provider and show that a price increase combined with a strong failure–to–supply clause leads to a Pareto improvement that is effective in addressing shortages. Another prevalent area of research is the role of intermediaries. For example, see Kouvelis, Xiao, and Yang (2015) on research on the pricing and formulary decisions of pharmacy benefit manufacturers and Burns and Lee (2008), Hu, Schwarz, and Uhan (2012), and Saha, Seidmann, and Tilson (2019) for the analysis of the role of group purchasing organizations.

There has been a shift toward value–based healthcare in the pharmaceutical industry. In particular, payers have increasingly employed outcome–based contracting with pharmaceutical companies. This purchasing strategy ties reimbursement to patient outcomes (i.e., companies are paid more when medicines work well). It is important to note that this type of reimbursement scheme relies on having the appropriate supporting technology and processes in place (i.e., the ability to accurately measure/monitor patient outcomes). Industry analysts and researchers have brought up various benefits and drawbacks of this reimbursement scheme. However, more work is needed to thoroughly evaluate the ramifications of this payment scheme for different stakeholders such as manufacturers, payers, and patients.

Special Health Services Supply Chains

We subcategorize special health services SCs into blood, organ transplantation, and vaccine supply chains.

2.9 Blood Supply Chains

Donated blood and blood products are used in the treatment of various conditions (such as anemia) and in blood transfusions for patients undergoing surgery or those who have suffered an injury. Figure 2.5 presents a representative blood SC resembling a diagram from Fontaine et al. (2009). In their paper, the authors discuss several distinguishing features of blood SCs. Blood cannot be

manufactured and can only originate from donors, which constrains supply. There is a lead time to blood utilization, because donated blood must undergo screening tests and needs to be processed before it can be transfused. Furthermore, the short shelf life of blood products (cryoprecipitate [cryo], plasma, red cells, whole blood, and platelets have a shelf life of one year, one year, up to forty–two days, twenty–one to thirty–five days, and five days, respectively [American National Red Cross 2020]) contributes to significant wastes resulting from outdated units. Last, mismatches between supply and demand frequently occur, leading to excess inventory (unused blood) or shortages. Several researchers have explored improvement opportunities in the collection, as well as the inventory management and allocation, of blood. Chung and Erhun (2013) consider supply contracts for blood with two periods of shelf life ("young" and "old" units). The authors demonstrate the channel coordinating conditions for three commonly employed industry contracts. For a thorough analysis of blood SCs, readers are referred to Pierskalla (2005).

Figure 2.5 A representative blood supply chain.

Ayer et al. (2019) state that because of the importance, limited supply, and perishability of blood products, effective management of blood collection is critical for high–quality healthcare delivery. The authors examine the cryo collection. They formulate a mathematical model to identify when and from which sites cryo should be collected such that weekly collection costs are minimized while at the same time ensuring that a weekly target is met. The authors' proposed collection model has since been implemented at the American Red Cross's largest manufacturing facility and the American Red Cross has realized significant benefits as a result of the implementation.

Regional blood banks supply hospitals in their service areas. Because of the scarcity of blood, it is common for regional blood banks to have to ration blood products among the hospitals they serve. Because of this supply uncertainty, hospitals tend to overorder to ensure a larger share of the rationed supply. Paul, Rajapakshe, and Mallik (2019) argue that overordering causes an increase in spoilage, which ultimately imposes a cost on the SC as well as a social welfare loss. They

demonstrate that a shortage–subsidy contract, which offers a per–unit subsidy for every unit of shortage experienced by a hospital, induces uninflated ordering by hospitals.

The management of blood, from collection to transfusion, is a critically important and often challenging undertaking. However, there is an extensive body of literature on the SCM of perishable products. Therefore, we underscore the potential to apply learnings and strategies from other sectors, such as the food industry, in the management of blood SCs and vice versa.

2.10 Organ Transplantation Supply Chains

Each year, hundreds of thousands of patients around the world wait for organs but only a fraction are lucky enough to undergo transplantation and many die each day waiting for a transplant because of a large gap between supply and demand. Organs can be removed for transplantation from living or deceased donors. Countries follow different policies (e.g., opt–in and opt–out policies) and the impact these policies have on donation rates has been a subject of great interest for researchers and policy makers. Exacerbating the shortage issue, not all organs donated are viable for use. Furthermore, in some cases, viable organs are wasted because of inefficiencies in the organ transplantation process caused by the level of coordination required across parties involved, such as ED units and intensive care unit staff (Barrow 2012). In addition, donated organs need to be matched to patients based on many factors, such as blood type, body size, and patient availability. Concerning living donor donations, Glorie et al. (2014) describe kidney exchanges in cycles, which allow multiple donors to donate their kidneys and multiple patients to receive kidneys that are compatible with their medical conditions. Unlike blood donations, organ donations require simultaneity to prevent organ donors from reneging after their intended recipient has received a transplant from another donor. Because of this simultaneity, the length of cycles is limited to the number of logistically feasible simultaneous transplants. A typical closed organ SC is one in which each station has an incompatible pair composed of a donor and a recipient. To form compatible matches, each patient receives an organ from the paired donor of another patient in a cyclic manner. Other organ SCs may have very different structures depending on the allocation mechanisms in place. For example, Su and Zenios (2006) discuss a kidney SC that is characterized by n transplant queues corresponding to n candidate types. Aside from simultaneity, another issue

concerning organ SCs is that there are significant disparities in the wait time and access to organs across geographical areas. To alleviate geographic inequality in the US context, Ata, Skaro, and Tayur (2017) propose the utilization of affordable jet services to enable patients to list in multiple, and possibly distant, donation service areas.

Altruistic or nondirected donations from living donors have also gained ground. NHS Blood and Transplant reports that since a change in the law a decade ago (permitting donors to give their organs to people they have never met), more than five hundred people have helped save the life of a stranger (NHS Blood and Transplant 2016). Altruistic donations can potentially multiply the number of recipients benefitting from each donation because they can link several pairs of incompatible donor and recipient pairs to form a donation chain. This domino effect works through the initiation of a chain of matches (an altruistic donation is matched to a recipient who has a willing but incompatible donor; consequently, the incompatible donor can give their organ to the next compatible recipient, and so on [Montgomery et al. 2006]). Researchers have evaluated organ exchange cycles and chains and have addressed the question of whether transplants should be performed simultaneously or nonsimultaneously. The severe shortage in available organs for transplantation is a clear catalyst for future research that aims to improve the obtainment, the matching of donors and recipients, and the allocation of organs.

2.11 Vaccine Supply Chains

One vaccine supply chain that is frequently studied in the operations management literature is the influenza vaccine SC. Influenza spreads rapidly around the world in seasonal epidemics and carries considerable financial and human implications (such as lost productivity). Vaccination protects against infection. In addition, it provides a positive externality, because vaccinated individuals decrease the infection risk of their close contacts, thus reducing the impact of outbreaks (Arifoglu, Deo, and Iravani 2012). Vaccine SCs resemble traditional SCs, with a key difference being that healthcare providers (such as hospitals and clinics) assume the role of retailers. Vaccine SCs exhibit two specificities: uncertain demand because of the unpredictability of flu prevalence and uncertain production yield arising from the biological composition of the vaccine. Further complicating matters, vaccine manufacturers do not decide on the composition of their vaccines.

Instead, an external committee determines the composition. For example, in the United States, the Vaccines and Related Biological Products Advisory Committee makes recommendations to the Food and Drug Administration about the annual vaccine composition in February or March of each year for the upcoming flu season that begins the following October (Dai, Cho, and Zhang 2016). Long lead times arise because of the complexity of vaccine production.

From a committee's perspective, Cho (2010) presents research to aid the decision between retaining the current virus strain, changing to a new strain, or deferring the decision. The choice to retain the current strain leads to lower production yield uncertainty, but at the same time runs the risk of being less effective should a new virus strain spread. Conversely, the choice to defer the decision offers the benefit of acquiring more information, thus reducing the risk that the wrong strain will be pursued. However, delaying the decision can result in a supply shortage. Cho (2010) offers an optimal threshold policy concerning the committee's decision. Dai, Cho, and Zhang (2016) analyze contracting in the influenza vaccine SC, where there is a trade–off between late and early vaccine production. The authors show that a properly designed buyback and late rebate contract can not only coordinate the SC but also allow for flexibility in the division of profits.

The idiosyncrasies of the vaccine SC have attracted substantial attention from operations management and SCM researchers. In recent years, there has been a rising interest in employing various data such as social media and online activity to forecast flu outbreaks. Predicting influenza activity can shed light on when healthcare practitioners can expect to see a rise in demand for their services. This, in turn, can assist providers in making operational decisions such as staffing. An example of this is Google Flu Trends, which monitored and analyzed Google search queries to estimate flu prevalence. The project was abandoned within a few years following issues related to the accuracy of predictions. With the growing popularity of big data, the Google Flu Trends case shows that caution is warranted. Researchers have pointed to "big data hubris"—the "assumption that big data are a substitute for, rather than a supplement to, traditional data collection and analysis"—to the downfall of Google Flu Trends (Lazer et al. 2014). Lazer et al. (2014) promote a focus on an "all data revolution" rather than a "big data revolution," one in which data from traditional and new sources are used to provide a deeper and more comprehensive understanding

of the world (Lazer et al. 2014). Future research should, therefore, aim to incorporate and combine various analytic tools and approaches to guide decision–making.

2.12 Concluding Remarks

The global population is on the rise and aging. There is an increasing burden of disease brought about by the prevalence of chronic conditions. Many individuals are living with multiple comorbidities and have complex needs. As a result, the healthcare sector faces serious clinical, operational, and financial challenges. To manage the population's health needs, great efforts are required for health maintenance, as well as for the prevention, diagnosis, and treatment of diseases. Well–functioning SCs underpin effective and efficient healthcare delivery. Therefore, how SCs are designed, operated, and managed carries importance for individuals' health status, life expectancy, and quality of life. For each discussed hSC, we have proposed avenues for future research. In the current landscape, we feel three key research areas have the potential to establish the provision of timely, high–quality, accessible, and equitable healthcare at a lower cost (Betcheva, Erhun, and Jiang 2020): shifting the focus of care from treatment to prevention, shifting care closer to patients' homes, and shifting from broad treatment to personalized/precision medicine. Research in these areas will need to focus on new models of care, new reimbursement schemes, and emerging health technologies and innovations. We refer the reader to Keskinocak and Savva (2020) and KC, Scholtes, and Terwiesch (2020), who discuss these research opportunities, among others, in their contemplation of the future of healthcare operations. We also refer the reader to Betcheva, Erhun, and Jiang (2020) for a framework that enables supply chain thinking in healthcare: a customer–focused, systems based, and strategically orientated approach that simultaneously considers clinical, operational, and financial dimensions, as well as a discussion on supply chain strategies that can be applied and tailored to healthcare by considering the sector's unique challenges and opportunities.

We foresee significant developments in hSCs in the future. In particular, we anticipate changes in the resources (including the workforce), the processes, and strategies, as well as the infrastructure of hSCs. It is reasonable to expect that more sophisticated medical technologies and devices will continually emerge with the rapid advancement of technology. This necessitates a workforce with

technical capabilities, and clinician training should reflect this. New technologies and innovations also offer significant opportunities for healthcare provision in the developing world. As an example, take organizations like Zipline that are delivering medical products (such as blood and medication) using drones. Furthermore, robotics and digital technologies are increasingly entering healthcare systems. This offers the potential to address staff shortfalls. For instance, physicians spend a portion of their time performing mundane tasks such as computer entries. Through automation and the downshifting of tasks to lower–tier personnel, physicians' time is protected for activities that add more value toward patient care. Technologies, such as artificial intelligence, are also supporting clinical decision–making.

With a focus on the patient as a whole, we expect care delivery to aim attention at health maintenance rather than the treatment of disease. Such a shift will require more meaningful patient involvement and a sense of responsibility for one's own health. This shift needs to be facilitated by healthcare providers, who should promote self–care by ensuring information and support are available and accessible. We also note that technology, such as wearable devices, can enable self–monitoring. Devices and developments in telemedicine can also change the infrastructure of hSCs. As care moves closer to patients' home, we envision that the Internet of things will take on a greater presence in healthcare delivery with a lesser amount of a patient's care to be delivered in hospital settings.

Furthermore, technology is altering how hSC members communicate and collaborate (Betcheva, Erhun, and Jiang 2020). Electronic data sharing allows providers to make collective decisions on shared information. To gain more value from increased connectivity, communication platforms should be integrated, and data should be standardized across providers. This ensures that professionals access the same data and speak the same language. Moreover, data quality should be bolstered by improving the richness and accuracy of entries. The wealth of patient data will also facilitate developments in personalized medicine and data driven (clinical and operational) decision–making. We note that more research is required on how to best utilize the accumulation of data. In addition, dealing with issues regarding confidentiality and data protection becomes key in ensuring patients' and providers' trust.

Overall, in managing the population's increasing healthcare needs, future hSCs need to promote a focus on health maintenance, pursue a holistic and collaborative approach to healthcare, and foster a tech–forward and innovative mindset.

References

Adida, E., F. Bravo. 2019. Contracts for healthcare referral services: Coordination via outcome–based penalty contracts. *Management Science* 65(1):1322–1341.

American National Red Cross. 2020. Blood components. Available at: https://www.redcrossblood.org/donateblood/how–to–donate/types–of–blood–donations/blood–components.html. Accessed July 10, 2019.

Arifoğlu, K., S. Deo, S.M.R. Iravani. 2012. Consumption externality and yield uncertainty in the influenza vaccine supply chain: Interventions in demand and supply sides. *Management Science* 58(6):1072–1091.

Ata, B., A. Skaro, S. Tayur. 2017. Organjet: Overcoming geographical disparities in access to deceased donor kidneys in the United States. *Management Science* 63(9):2776–2794.

Ayer, T., C. Zhang, C. Zeng., C.C. White III, V.R. Joseph. 2019. Analysis and improvement of blood collection operations. *Manufacturing & Service Operations Management* 21(1):29–46.

Barrow, M. 2012. Patients die waiting for organs that go to waste. *The Times (London)*, January 30, 2012.

Beech, J., S. Bottery, A. Charlesworth, H. Evans, B. Gershlick, N. Hemmings, C. Imison et al. 2019. *Closing the gap—key areas for action on the health and care workforce.*" The Health Foundation, the King's Fund, Nuffield Trust, March 19, 2019. Available at: https://www.kingsfund.org.uk/publications/closing–gap–health–care–workforce.

Betcheva, L., F. Erhun. 2018. *"Which stage of the industry lifecycle do clinical research organizations (CROs) currently reside in? An exploratory analysis using clinical trials data."* MRes Diss., Judge Business School, University of Cambridge. Available upon request from the authors.

Betcheva, L., F. Erhun, H. Jiang. 2021. Supply chain thinking in healthcare: Lessons and outlooks. *Manufacturing & Service Operations Management* 23(6):1333–1353.

Bhattacharya, S., V. Gaba, S. Hasija. 2015. A comparison of milestone based and buyout options contracts for coordinating R&D partnership. *Management Science* 61(5):963–978.

Blouin, R.A., M.L. Adams. 2017 The role of the pharmacist in health care: Expanding and evolving. *North Carolina Medical Journal* 78(3):165–167.

Blumberg, D.F. 2004. New strategic directions in acquiring and outsourcing high–tech services by hospitals

and implications for clinical engineering organizations and ISOs. In *Clinical Engineering Handbook*, edited by Joseph F. Dyro, 137–146. Academic Press Series in Biomedical Engineering. Cambridge, MA: Elsevier Academic Press.

Bottery, S., M. Varrow, R. Thorlby, D. Wellings. 2018. A fork in the road: Next steps for social care funding reform. The Health Foundation and the King's Fund. May 2018. Available at: https://www.kingsfund.org.uk/sites/default/files/2018–05/Afork–in–the–road–next–steps–for–social– care–funding–reform–May–2018.pdf.

Bretthauer, K.M., S.H. Heese, H. Pun, E. Coe. 2011. Blocking in healthcare operations: A new heuristic and an application. *Production and Operations Management* 20(3):375–391.

Brindle, D. 2017. Buurtzorg: The Dutch model of neighbourhood care that is going global. *The Guardian*, May 9, 2017. Available at: https://www.theguardian.com/social–care network/2017/may/09/buurtzorg–dutch–model–neighbourhood–care.

Burns, L.R., J.A. Lee. 2008. Hospital purchasing alliances: Utilization, services, and performance. *Health Care Management Review* 33(3):203–215.

Calsyn, M., E.O. Lee. 2012. *Alternatives to fee–for–service payments in health care*. *Center for American Progress.* September 2012. Available at: https://www.americanprogress.org/wp–content/uploads/2012/09/FeeforService–1.pdf.

Chan, T.H., F. de Véricourt, O. Besbes. 2019. Contracting in medical equipment maintenance services: An empirical investigation. *Management Science* 65(3):1136–1150.

Charles, A. 2019. Community health services explained. The King's Fund. January 14, 2019. Available at: https://www.kingsfund.org.uk/publications/community–health–services–explained#how–are–they–organised.

Charlesworth, A., P. Johnson. 2018 *Securing the future: Funding health and social care to the 2030s.* London: Institute for Fiscal Studies, Health Foundation.

Cho, S–H. 2010. The optimal composition of influenza vaccines subject to random production yields. *Manufacturing & Service Operations Management* 12(2):256–277.

Christopher, M.L. 2016. *Logistics and supply chain management*. 5th ed. Harlow, England: Pearson Education.

Chung, Y.T., F. Erhun. 2013. Designing supply contracts for perishable goods with two periods of shelf life. *IIE Transactions* 45(1):53–67.

Cruz, A.M., A.M.R. Rincon. 2012. Medical device maintenance outsourcing: Have operation management research and management theories forgotten the medical engineering community? A Mapping Review. *European Journal of Operational Research* 221(1):186–197.

Dai, T., S–H. Cho, F. Zhang. 2016. Contracting for on–time delivery in the U.S. influenza vaccine supply
chain. *Manufacturing & Service Operations Management* 18(3):332–346.

de Vries, J., R. Huijsman. 2011 Supply chain management in health services: An overview. *Supply Chain Management: An International Journal* 16(3):159–165.

DiMasi, J.A., H.G. Grabowski, R.W. Hansen. 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics* 47:20–33.

Ertem, M.A., N. Buyurgan, M.D. Rossetti. 2010. Multiple–buyer procurement auctions framework for humanitarian supply chain management. *International Journal of Physical Distribution & Logistics Management* 40(3):202–227.

Fontaine, M.J., Y.T. Chung, W.M. Rogers, H.D. Sussmann, P. Quach, S.A. Galel, L.T. Goodnough, F. Erhun. 2009. Improving platelet supply chains through collaborations between blood centers and transfusion services. *Transfusion* 49(10):2040–2047.

Freeman, M., S. Robinson, S. Scholtes. 2021. Gatekeeping, fast and slow: An empirical study of referral errors in the emergency department. *Management Science* 67(7):4209–4232.

Gershlick, B., Z. Firth. 2017. Provision of community care: Who, what, how much? The Health Foundation Briefing, May 2017. Available at: https://www.health.org.uk/publications/provision–of–community– care–who–what–how–much.

Glorie, K.M., J.J. van de Klundert, A.P.M. Wagelmans. 2014. Kidney exchange with long chains: an efficient pricing algorithm for clearing barter exchanges with branch–and–price. *Manufacturing & Service Operations Management* 16(4):498–512.

Health Foundation, Nuffield Trust, the King's Fund. 2018. The health care workforce in England–make or break? November 15, 2018. Available at: https://www.kingsfund.org.uk/publications/health–care–workforce–england.

Healx. 2019. Accelerating treatments for rare diseases. Available at: https://healx.io/. Accessed July 5, 2019.

Hu, Q., L.B. Schwarz, N.A. Uhan. 2012. The impact of group purchasing organizations on healthcare–product supply chains. *Manufacturing & Service Operations Management* 14(1):7–23.

Jain, N., S. Hasija, D.G. Popescu. 2013. Optimal contracts for outsourcing of repair and restoration services. *Operations Research* 61(6):1295–1311.

Jia, J., H. Zhao. 2017. Mitigating the U.S. drug shortages through pareto–improving contracts. *Production and Operations Management* 26(8):1463–1480.

Jiang, H., Z. Pang, S. Savin. 2012. Performance–based contracts for outpatient medical services. *Manufacturing & Service Operations Management* 14(4):654–669.

Joynt, K.E., J.F. Figueroa, J. Oray, A.K. Jha. 2016. Opinions on the hospital readmission reduction program: Results of a national survey of hospital leaders. *American Journal of Managed Care* 2(8):e287–294.

Karmarkar, U.S., G. Roles. 2015. An analytical framework for value co–production in services. *Service Science* 7(3):163–180.

Kavadias, S., K. Ladas, C.H. Loch. 2016. The transformative business model. *Harvard Business Review* 94(October):91–98.

KC DS, Scholtes S, Terwiesch C (2020) Empirical research in healthcare operations: Past research, present understanding, and future opportunities. *Manufacturing & Service Operations Management* 22(1):73–83.

Keskinocak, P., N. Savva. 2020. A review of the healthcare–management (modeling) literature published in *Manufacturing and Service Operations Management*. *Manufacturing & Service Operations Management* 22(1):59–72.

Kim, S–H., I–W.G. Kwon. 2015. The study of healthcare supply chain management in United States: Literature review. *Management Review: An International Journal* 10(2):34–56.

King's Fund. 2018. Key challenges facing the adult social care sector in England. December 12, 2018. Available at: https://www.kingsfund.org.uk/publications/key–challenges–facing–adult–social–care–sector–England.

Kouvelis, P., J. Milner, Z. Tian. 2017. Clinical trials for new drug development: Optimal investment and application. *Manufacturing & Service Operations Management* 19(3):437–452.

Kouvelis, P., Y. Xiao, N. Yang. 2015. PBM competition in pharmaceutical supply chain: Formulary design and drug pricing. *Manufacturing & Service Operations Management* 17(4):511–526.

Lazer, D., R. Kennedy, G. King, A. Vespignani. 2014. The parable of Google Flu: Traps in big data analysis. *Science* 343(6176):1203–1205.

Lu, L.X., S.F. Lu. 2018. Distance, quality, or relationship? Interhospital transfer of heart attack patients. *Production and Operations Management* 27(12):2251–2269.

Lu, S.F., H. Rui, A. Seidmann. 2018. Does technology substitute for nurses? Staffing decisions in nursing homes. *Management Science* 64(4):1842–1859.

Malkin, R.A., C. Whittle. 2014. Biomedical equipment technician capacity building using unique evidence–based curriculum improves healthcare. *Journal of Clinical Engineering* 39(1):37–44.

Medical Futurist. 2018. Could A.I. solve the human resource crisis in healthcare? August 2, 2018. Available at: https://medicalfuturist.com/could–a–i–solve–the–human–resources–crisis–in–healthcare.

Mentzer, J.T., W. DeWitt, J.S. Keebler, S. Min, N.W. Nix, C.D. Smith, Z.G. Zacharia. 2001. Defining supply chain management. *Journal of Supply Chain Management* 22(2):1–25.

Montgomery, R.A., S.E. Gentry, W.H. Marks, D.S. Warren, J. Hiller, J. Houp, A.A. Zachary et al. 2006. Domino paired kidney donation: A strategy to make best use of live non–directed donation. *Lancet* 368(July):419–421.

Narayana, S.A., R.K. Pati, P. Vrat. 2014. Managerial research on the pharmaceutical supply—A critical review and some insights for future directions. *Journal of Purchasing & Supply Management* 20(1):18–40.

National Collaboration for Integrated Care and Support. 2013. *Integrated care and support: Our shared commitment.* May 2013. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/198748/DEFINITIVE_FINAL_VERSION_Integrated_Care_and_Support_–Our_Shared_Commitment_2013–05–13.pdf.

National Institute for Health Research. 2019. Physician associates an asset to hospital and surgical teams, study finds. February 4, 2019. Available at: https://www.nihr.ac.uk/news/physician–associates–an–asset–to–hospital–medical–and–surgical–teams–studyfinds/11402.

NHS Blood and Transplant. 2016. 500 People have now donated a kidney to a stranger. September 21, 2016. Available at: https://www.organdonation.nhs.uk/get–involved/news/500–people–have–now–donated–a– kidney–to–a–stranger/.

NHS Digital. 2017. Adult social care activity and finance report, England 2016–17. October 25, 2017. Available at: https://digital.nhs.uk/catalogue/PUB30121.

NHS England. 2013. Transforming urgent and emergency care services in England. November 2013. Available at: https://www.nhs.uk/NHSEngland/keogh–review/Documents/safer–faster–better–v28.pdf.

NHS England. 2019. The physician associate will see you now—new role to assist patients in primary care. Accessed July 15, 2019. Available at: https://www.england.nhs.uk/gp/case–studies/the–physician–associate–will–see–you–now–new–role–to–assist–patients–inprimary–care/.

NHS Improvement. 2017. Case studies: Focus on improving patient flow. July 2017. Available at: https://improvement.nhs.uk/documents/1428/Patient_Flow_Guidance_Case_studies_13_July.pdf

Oloruntoba, R., R. Gray. 2006. Humanitarian aid: An agile supply chain? *Supply Chain Management: An International Journal* 11(2):115–120.

Organisation for Economic Co–operation and Development. 2016. *Health workforce policies in OECD countries: Right jobs, right skills, right places*. Paris: OECD Health Policy Studies, OECD. http://dx.doi.org/10.1787/9789264239517–en.

Oxtoby, K. 2009. Professional roles are blurring. *The British Medical Journal* 338(January):a3163. https://doi.org/10.1136/bmj.a3163.

Parvin, H., S. Beygi, J.E. Helm, P.S. Larson, M.P. Van Oyen. 2018. Distribution of medication considering information, transshipment, and clustering: Malaria in Malawi. *Production and Operations Management* 27(4):774–797.

Paul, A., T. Rajapakshe, S. Mallik. 2019. Socially optimal contracting between a regional blood bank and hospital. *Production and Operations Management* 28(4):908–932.

PhRMA. 2016. 2016 Biopharmaceutical research industry profile. April 2016. Available at: http://phrmadocs.phrma.org/sites/default/files/pdf/biopharmaceutical–industry–profile.pdf.

Pierskalla, W.P. 2005. Supply chain management of blood banks. In *Operations Research and Health Care*, edited by Margaret L. Brandeau, François Sainfort, and William P. Pierskalla, 103–45. Vol. 70 of *International Series in Operations Research & Management Science*. Boston: Springer.

Privett, N., D. Gonsalvez. 2014. The top ten global health supply chain issues: Perspectives from the field. *Operations Research for Health Care* 3:226–230.

Rafols, I., M.M. Hopkins, J. Hoekman, J. Siepel, A. O'Hare, A. Perianes–Rodríguez, P. Nightingale. 2014. Big pharma, little science? A bibliometric perspective on big pharma's R&D decline. *Technological Forecasting & Social Change* 81:22–38.

Royal College of Nursing. 2016. The Buurtzorg nederland (home care provider) model: Observations for the United Kingdom (UK). RCN Policy and International Department policy briefing. April 2016. Available at: https://www.rcn.org.uk/–/media/royal–college–ofnursing/documents/policies–and–briefings/uk–wide/policies/2015/br–0215.pdf.

Saha, R.L., A. Seidmann, V. Tilson. 2019. The impact of custom contracting and the infomediary role of healthcare GPOs. *Production and Operations Management* 28(3):650–667.

Savva, N., S. Scholtes. 2014. Opt–out options in new product co–development partnerships. *Production and Operations Management* 23(8):1370–1386.

Stylianou, N., R. Fackrell, C. Vasilakis. 2017. Are medical outliers associated with worse patient outcomes? A retrospective study within a regional NHS hospital using routine data. *BMJ Open* 7(5):e015676.

Su, X., S.A. Zenios. 2006. Recipient choice can address the efficiency–equity trade–off in kidney transplantation: A mechanism design model. *Management Science* 52(11):1647–1660.

Trebble, T.M., N. Hansi, T. Hydes, M.A. Smith, M. Baker. 2010. Process mapping the patient journey: An introduction. *BMJ* 341:c4078.

Wagner, S.M., B. Thakur–Weigold. 2018. Supporting collaboration in humanitarian supply chains—insights from a design science project. *Production Planning & Control* 29(14):1130–1144.

Wang, D., D.J. Morrice, K. Muthuraman, J.F. Bard, L.K. Leykum, S.H. Noorily. 2018. Coordinated scheduling for a multi–server network in outpatient pre–operative Care." *Production and Operations Management* 27(3):458–479.

World Health Organization. 2011. *Medical equipment maintenance programme overview*. Geneva: World Health Organization.

Chapter 3

Supply Chain Thinking in Healthcare: Lessons and Outlooks

3.1 Introduction

A supply chain (SC) is a "network of organizations that are involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services in the hands of the ultimate consumer" (Christopher 2016, p. 13). Supply chain management (SCM) is the "management of upstream and downstream relationships with suppliers and customers in order to deliver superior customer value at less cost to the supply chain as a whole" (Christopher 2016, p. 3).

Since the term was coined in the early 1980s, SCM has risen to prominence and, with decades of theoretical and practical wisdom attached to it, it is now the backbone of business. With a marked focus on the interactions between stakeholders, the wealth of acquired SCM knowledge provides a unique opportunity to understand, evaluate, and improve complex ecosystems such as healthcare systems. This, of course, begs the question: How can we adopt well–known strategies from more traditional SCs to healthcare ecosystems? For example, how can we replicate Amazon's customer obsession in building patient– and provider–centric care delivery? How can Zara's lean and agile SCs, which satisfy their functional and innovative product needs, respectively, show us how to separate routine and complex care in hospitals? How can we extend the partnership model that enabled P&G to be a "part of Walmart" to promote integrated care through performance improvement and benefit sharing?

This essay is based on the paper: Betcheva, L., F. Erhun, and H. Jiang. 2020. Supply Chain Thinking in Healthcare: Lessons and Outlooks. Manufacturing & Service Operations Management, 23(6):1333–1353.

3.1.1 Supply Chain Thinking in Healthcare: A Framework

At the core of efficient and effective SCM is supply chain thinking, which includes three key aspects: a customer focus, a systems approach, and a strategic orientation (Mentzer et al. 2001). A *customer focus* ensures that the creation of customer value is the key driver of the SC's activities. A *systems approach* views the organizations in the SC as an end–to–end, integrated entity while each individual organization's *strategic orientation* aligns the intra– and interfirm goals and capabilities of the organization with those of the SC. Yet, as we will discuss in Section 3.1.4, healthcare faces unique challenges that sometimes deviate from the difficulties found in other ecosystems. For instance, a stark difference emerges from the fact that because their health is and their lives are potentially at stake, patients, who are the end consumers in healthcare SCs (hSCs), have distinct vulnerabilities, needs, and demands compared with customers of other goods and services. This also calls for simultaneous consideration of the clinical, operational, and financial dimensions of any healthcare research or practical initiative. That is, one can broadly conceptualize healthcare SCM (hSCM) as the adaptation of supply chain thinking within the realm of healthcare (Figure 3.1).

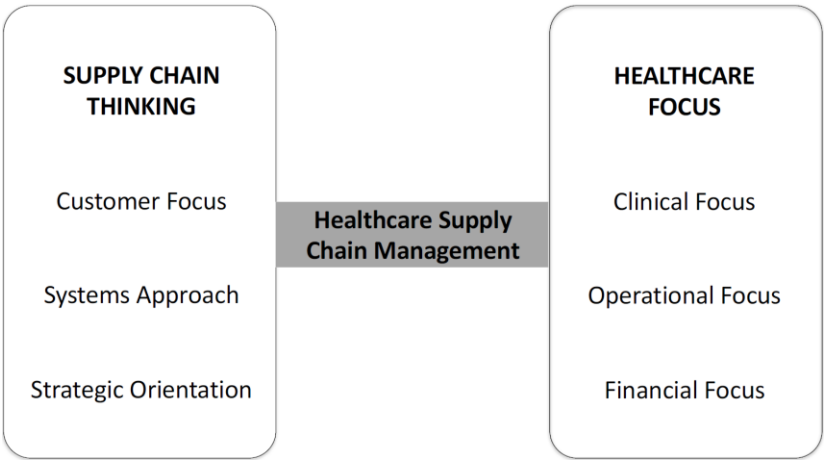

Figure 3.1 Healthcare SCM requires a customer focus, systems approach, and strategic orientation (Mentzer et al. 2001) with simultaneous consideration of clinical, operational, and financial implications.

The *clinical* dimension ensures that any move from a more traditional model to a hSCM model does not diminish the safety, outcomes, or experiences provided to end users. Any action or change

within a healthcare system should be motivated and guided by the needs and requirements of patients. However, the clinical dimension does not only include individual patients but also the patient–clinician interaction, which is the principal transaction in healthcare. Therefore, whenever hSCM is adopted, it is also important to account for its consequences for clinicians' work, morale, and job satisfaction. Failing to do so can lead to burnout and reduce the most basic supply factor–clinician time (Betcheva et al. 2019, Charles 2019). The *operational* dimension comprises the technologies and care models that enable operationalization of the transformation. In considering this dimension, decision makers must ask whether the right information and resources are in the right place and applied at the right time to ensure care is provided in the most effective and efficient way. For example, this entails determining which providers treat which patients and when (points of care), where (e.g., in hospitals, in outpatient clinics, at home), and how (e.g., surgery, physical therapy) treatment takes place. Finally, due consideration of the *financial* dimension ensures the cost–effectiveness of the improvement and requires creation and placement of appropriate incentives. For instance, provider reimbursement has become particularly important to the effective functioning of new care delivery models, such as accountable care organizations (ACOs). Only when a transformation creates a simultaneous win–win–win in the clinical, operational, and financial dimensions can we expect it to be successfully implemented and sustained in healthcare ecosystems.[1] Healthcare SCM can be instrumental in achieving this win–win–win.

3.1.2 Healthcare Supply Chain Management: A Broader View

Historically, hSCs have commonly been associated with the procurement and logistics of healthcare supplies and services. However, recent developments in healthcare render this understanding too narrow. For example, new ways of thinking, as illustrated by widespread technology adoption, a focus on integrated care delivery, and an emphasis on aligning stakeholder interests through new reimbursement schemes, have primed healthcare management for the introduction of broader SC concepts. In addition, the complexity in the interactions across

[1] Discussions in the medical community highlight the importance of jointly considering these factors. For example, Berwick et al. (2008) emphasize the triple–aim of healthcare as enhancing clinical outcomes and user experience while controlling costs. Similarly, despite its popularity, Dartmouth Atlas (2019) has become controversial in debates for ignoring factors such as outcomes and illness severity and only focusing on cost in their efficiency measures (Bach 2010).

healthcare stakeholders and the siloed nature of care delivery create an opportunity to understand, evaluate, and improve this inefficient ecosystem in a systematic, holistic manner. Thus, following the path of traditional SCs, which have expanded the scope of purchasing to the prevailing view of SCM (Kraljic 1983), hSCM, as we define it, has a much broader scope than the usual procurement– and logistic–focused definition. In adopting this broader view, we define *healthcare supply chain management* as the management of people, processes, information, and finances to deliver medical products and services to consumers, in the pursuit of enhancing clinical outcomes and user experience, while controlling costs (Berwick et al. 2008, de Vries and Huijsman 2011, Betcheva et al. 2019). Within our definition, people can refer to patients, providers, purchasers, and payers while processes can include patient flow, clinical development, and blood collection and distribution. Information can take the form of diagnoses, treatment plans, patient generated data, and so on, whereas finances can comprise costs, payments, and reimbursements. Medical products can include pharmaceuticals, medical devices, and health aids, whereas services can encompass curative, preventive, rehabilitative, and palliative care. As the end goal of this supply chain, healthcare delivery (i.e., the provision of healthcare services including, but not limited to, the prevention, diagnosis, treatment, and management of illness) hinges on the joint efforts of and interactions between various stakeholders. Table 3.1 lists these stakeholders, including organizations and individuals, and Figure 3.2 provides a high–level representation of the interactions between stakeholders.

Table 3.1 hSC Organizational and Individual Stakeholders (The King's Fund 2013, PhRMA 2016).

Category	Stakeholders
End consumers	Patients, patient families, and populations
Care providers	Hospitals, clinics, ambulance services, community care, social care, nursing homes, informal care, mental health, public health, dental care, physicians, nurses, technicians, managers, paramedics, dentists, psychiatrists
Intermediaries	Group purchasing organizations, pharmacy benefit managers
Pharmaceutical providers	Innovators (such as research institutes and academia), biotechnology firms, clinical trial sites, raw material suppliers, pharmaceutical manufacturers, distributors, wholesalers, pharmacies (retailers)
Equipment and ancillaries	Medical, diagnostic, and surgical devices, capital equipment, office equipment, vaccines, blood, organs
Contractors	Contract research organizations, contract manufacturing organizations, site management organizations, clinical commissioning groups
Policy makers	Governments, regulators, patent and trademark offices, quality monitors, advisory committees, lobbyists
Payers	Insurance companies, national and local governments, employers, venture capital firms, communities, nonprofit organizations, foundations and charities, patients, patient families
Support services	National Institute of Health Research, NHS Improvement, research institutes, independent and charitable think tanks, MedTech including information technology systems and electronic health records, decision support systems

As the recipients of healthcare, patients, for the most part, interact exclusively with care providers: they consult with their primary care physicians, receive treatment from nurses and doctors within and outside of hospitals, and obtain prescription medications from pharmacists. To perform their duties, care providers need access to pharmaceuticals, supplies, equipment, and ancillaries. Stakeholders, such as pharmaceutical companies, medical, diagnostic, and surgical device manufacturers, and blood centers, among many others, interact with care providers (often through intermediaries such as group purchasing organizations) to ensure the provision of such products and services. Policymakers govern these interactions. For instance, the Food and Drug Administration in the United States regulates the testing, manufacturing, and marketing of drugs. Interactions between stakeholders are facilitated by both payers (which provide finances) and support services (which provide information). That is, a multitude of different entities enable care providers to execute their functions. We can categorize these entities into various SCs (such as health services and pharmaceuticals), all of which play unique, interrelated roles in care delivery. We refer readers to the supplemental material for a categorization of hSCs and a synopsis of research for each hSC subcategory and to Betcheva et al. (2019) for details of the main challenges and risks faced by different hSCs.

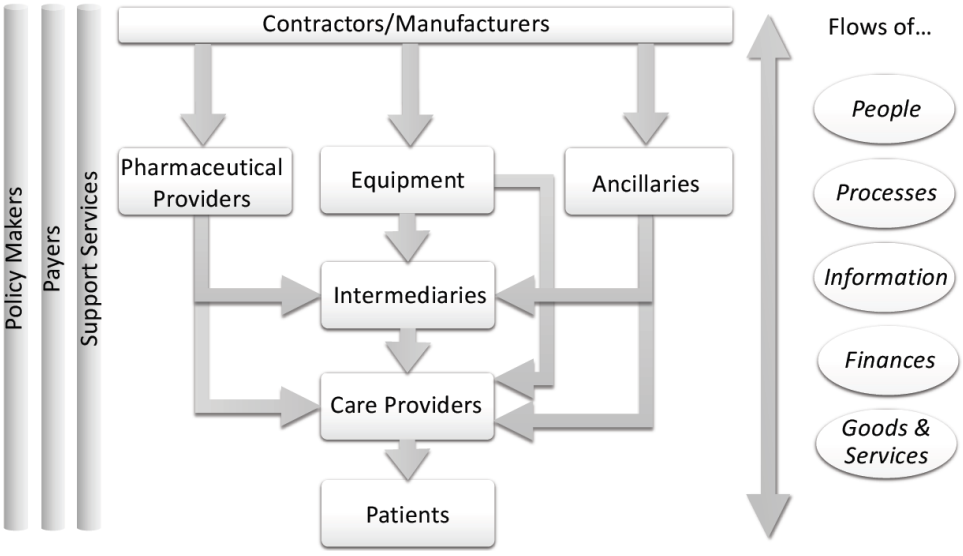

Figure 3.2 Schematic of the interactions between stakeholders and the flow of people, processes, information, finances, and products and services in the hSC.

3.1.3 Supply Chain Thinking: Exemplars

Numerous examples demonstrate that, with supply chain thinking, healthcare organizations can decrease costs and improve the quality of care by uncovering, quantifying, and addressing inefficiencies. Driven by a mission to eradicate unnecessary blindness in India and to provide healthcare for all, the Aravind Eye Care System (motivated by McDonald's food assembly lines) fully aligns its delivery systems with its strategy. With a focus on patients, the utilization of a systems approach (e.g., the creation of a hub–and–spoke ecosystem through the use of telemedicine) and a strategic orientation (e.g., Aurolab, Aravind's manufacturing arm, was established to manufacture intraocular lenses at high volume in order to decrease costs), Aravind delivers cataract care in India at 1% of the cost of cataract care in the United Kingdom's national health service (NHS) (Vickers and Rosen 2011).

By combining the elective orthopedic services of five district hospitals into one high–volume excellence center, Finland's Coxa Hospital provides a one–stop shop for patients in a site purpose–built around the main patient pathways. Coxa is able to achieve high clinical (e.g., low infection and revision rates), operational (e.g., fast procedure turnaround time, high operating room utilization), and financial outcomes (cost savings passed onto consumers in the form of lower prices) as a result of standardization coupled with high volumes, information sharing (e.g., cross organizational shared electronic health records (EHRs) and transparency of surgeon–level performance data) (Dowdeswell and Vauramo 2009, Gov.uk 2010, Coxa 2017), and incentive mechanisms that align patients' goals with operational capabilities (such as reimbursing patients for avoidable complications).

Over the course of more than 15 years using principles drawn from the famous Toyota Production System, the Virginia Mason Production System (VMPS) was established by Virginia Mason Health System (Virginia Mason 2019). With a focus on the entire system, the inclusion of patients and their families in the transformation and the alignment of stakeholder expectations around Virginia Mason's shared vision have all become essential to the success of the continuously changing and learning environment of VMPS. VMPS improves quality and safety, reduces the

burden of work for team members, and decreases the cost of providing care (Virginia Mason Medical Center 2010, Kenney 2011).

The benefit of supply chain thinking in healthcare has also been recognized in the academic literature. Recently, Dai and Tayur (2020) have argued that "the field of healthcare operations management (HOM) … has started to look beyond point–level operational improvements and examine the interactions of multiple entities, shifting our gaze onto the healthcare ecosystem" (p. 1). Their paper (which uses *ecosystem* to describe what we refer to as healthcare SC) focuses on reviewing methodological tools commonly used in HOM and on classifying research problems. In contrast, we aim to provide an understanding of how broader SCM concepts and strategies can be applied and tailored to healthcare by considering the sector's unique challenges and opportunities, and we also offer guidance to practitioners and possible research directions for the hSCM community. Our goal, in other words, is to provide a primer on supply chain thinking in healthcare. We therefore do not present a detailed literature review; we refer readers to Keskinocak and Savva (2020) and KC et al. (2020) for thorough reviews of the healthcare operations literature from a modeling point of view and an empirical point of view, respectively.

Our paper further contributes to the existing literature by building on the work of Green (2012) and Pinker (2012). Green argues that the growing availability of operational, financial, and patient data paves the way for HOM researchers to work with healthcare providers to establish evidence–based healthcare. Pinker further develops this argument by encouraging more ambitious goals and a wider range of research opportunities for HOM researchers. In this paper, we shift the focus to the *interactions* and *relationships* among a multitude of entities in healthcare ecosystems and anchor our framework in *supply chain thinking*. We broaden the scope of hSCM and advocate for further involvement of SCM scholars in the healthcare domain.

3.1.4 Challenges in Healthcare Delivery

Similar to traditional SCs, challenges such as variability, inflexibility, and waste (Cachon and Terwiesch 2009) are commonly observed in hSCs, making their management taxing. In addition, compared with SCs in other ecosystems, management of hSCs sometimes presents unique

difficulties. In Table 3.2, we provide an overview of the main clinical and public health, operational, and financial challenges in hSCs. We discuss these challenges in greater detail in the supplementary material. Table 3.3 displays commonly used reimbursement methods and the main criticisms of each method. We note that, although the healthcare sector is focused on the treatment of disease in individuals, it simultaneously plays a central role in the domain of public health. Public health focuses on measures related to the prevention (reducing the incidence of ill health), protection (preventing the spread of communicable disease), and promotion (enabling people to lead healthier lifestyles) of health (Royal College of Nursing 2020). A closely related approach, population health, aims to improve health outcomes and reduce health inequalities across an entire population by addressing social, cultural, political, economic, commercial, and environmental determinants of health (Buck et al. 2018, Lovell and Bibby 2018). An aging population, rising prevalence of chronic disease, and widening health inequalities highlight the need for effective joint functioning of healthcare delivery and public health. Studying the public health component of healthcare ecosystems would create an opportunity to deliver care at a lower cost and would lead to a better understanding and more accurate characterizations of the longer–term outcomes of care delivery.

Table 3.2 Clinical and public health, operational, and financial challenges in hSCs.

Challenge	Description	Implications	Opportunities
1. Clinical and public health			
1.1 Uncertainty	Uncertainty in the disease definition, diagnosis, prognosis, treatment plan and outcome evaluation due to probability, ambiguity and complexity	Can complicate and introduce variation in clinical decision making	Understanding and classifying uncertainty as groundwork for effective uncertainty management strategies
1.2 Medical errors	Preventable acts occurring as a result of actions not taken or as a result of the wrong actions taken encompassing preventive, diagnostic, and surgical care and treatment as well as device, equipment, and communication errors or failures	May result in unintended consequences for the patient (e.g., adverse effects)	Can be mitigated by various operational strategies and safeguards, such as the standardization of procedures (Ramdas et al. 2018)
1.3 Coproductive nature of healthcare	Achieving safe and effective care depends on the efforts of both patients and providers	Poor patient adherence can compromise the treatment efforts of providers and jeopardize safety and health outcomes	Better care through improved patient engagement and provider receptiveness of patient preferences
1.4 Investment tradeoffs	Central trade-off between investment in upstream public health interventions associated with longer, healthier lives and spending for downstream short-term needs related to the treatment of disease (Finch et al. 2018, Marshall et al. 2018)	Although many factors that contribute to noncommunicable disease are behavioral, and therefore preventable, only a small fraction of health spending (3% in OECD countries) goes toward preventive services (Gmeinder et al. 2017)	Evidence of the impact of public health interventions are limited compared with healthcare interventions
1.5 Complexity of population health	Influenced by many health and socioeconomic factors and there can be a multidirectional and dynamic relationship between those factors	Can complicate the design and evaluation of population health interventions	Studying the public health component of healthcare ecosystems would create an opportunity to deliver care at a lower cost
	Spillover effects on others, such as family members	Effects of public health initiatives may take many years to become apparent	
2. Operational			
2.1 Delegated decision making	Care providers make consumption decisions on behalf of patients, thus making the puchasing decisions for them as a third-party agent	Patient experience can come under threat if patient wants, preferences and expectations are not factored into care decisions	Patients should ideally be partners in designing their care processes
2.2 Third-party financing	Payers provide reimbursement for the products and services charged by providers. Patients and providers are "insulated from the price of the product or service" (wikipedia.com/health economics)	Payers are not fully privy to patients' health status (leading to adverse selection or hidden information) nor to providers' actions (leading to moral hazard or hidden action)	Carefully designed incentive and payment mechanisms Greater transparency between patients, providers and payers
2.3 Information asymmetry	Patients' complex needs require expert services yet patients are rarely in a position where they have complete information or the requisite knowledge to assess the quality of the service they receive	Creates a paternalistic care environment leading to potential power imbalances	Reinforced patient activation and more effective communication between patients and providers
2.4 Ambiguous and inaccurate performance measures	Lack of patient-level cost information due to opaque cost allocations	Challenging to quantify the value of healthcare and identify quality measures that are meaningful for physicians and patients alike	Data integration and transparency A greater focus on delivering value (considering both outcomes and costs)

Table 3.2 (Continued)

Challenge	Description	Implications	Opportunities
2.5 Pervasiveness of fragmented care	Difficult to assess the value or utility of healthcare due to the fact that is a healthcare is a credence,[a] merit,[b] and social[c] good and health of a human being is at stake	Wastes such as duplicative and nonvalue adding functions and inefficiencies caused by supply-driven demand	Increased coordination, data integration and adoption of end-to-end applications
	Siloed care and uncoordinated care delivery across organizations	Suboptimal patient safety and experience	
3. Financial			
3.1 Incentives from payment schemes	Payment methods can incentivize or disincentivize patients and providers influencing care utilization and care decisions	Wasted resources from overtreatement, overconsultation, overdiagnosis and overprescription	Increased implementation of outcome- and value-based reimbursement schemes facilitated by advancement and adoption of health technologies which diminish the burden of data collection and measurement
		Market failures such as the underuse of services and upcoding	

[a]A credence good is "a type of good with qualities that cannot be observed by the consumer after purchase, making it difficult to assess its utility" (investopedia.com).
[b]A merit good is "a type of good which, when consumed, provides external benefits, although these may not be fully recognized" (economicsonline.co.uk).
[c]A social good is a type of good whose value extends beyond the return to shareholders and benefits the wider society.

Table 3.3 Payment Methods in Healthcare.

Payment method	Definition	Example	Criticisms
Fee-for-service (FFS)	Providers are paid a fixed fee for each service provided	Australia's GP consultation fees under Medicare	Encourages providers to overtreat
Pay-per-diem (bundled payment)	Providers are paid a fixed amount for each patient visit/patient day (for inpatient services)	Hospital outpatient	Encourages providers to increase number of admissions and/or the length of stay
Case-based (bundled payment)	Providers are paid a fixed amount for admission or discharge depending on the patient and clinical characteristics	Hospital inpatient (DRGs - diagnosis-related groups)	Encourages providers to curtail costs by utilizing less (and/or less expensive) procedures, tests, and treatments and by engaging in upcoding
Population-based (Capitation)	A system of providers is paid in advance to provide a set of services for each patient enrolled	NHS Primary and Acute Care Systems (PACS),[a] U.S. Veterans Health Administration[b]	Encourages providers to enroll as many patients as possible, stint on care, cherry-pick healthier patients
Global budget	Providers are paid a fixed amount to deliver a set of services for a specified population over a defined period of time	Maryland's Global Budget Program,[c] Cambridge University Hospitals	Encourages providers to ration services Provides no incentive to attract more patients through improved performance
Performance-based (e.g., P4P)	Providers are paid for meeting certain performance measures	NHS Quality and Outcomes Framework,[d] Hospital Readmissions Reduction Program (HRRP)[e]	Unintended consequences of predetermined performance targets (see discussion on HRRP in Section 2.5)
Outcomes-based	Payment is linked to health indicators and outcomes (including patient-reported outcomes)	Amgen and Harvard Pilgrim's refund contract for Repatha[f]	The cost and difficulty of collecting timely, objective, and complete data on outcomes
Value-based	Payment depends on the value (where value accounts for outcomes and costs)	Centers for Medicare and Medicaid Services Hospital Value-Based Purchasing Program[g]	The complexity of defining and the burden of measuring and reporting outcomes and costs

Source. Adapted from https://www.who.int/healthfinancing/topics/purchasing/payment-mechanisms/en/.
[a]We refer the reader to NHS England (2016) for an overview of PACS.
[b]We refer the reader to Oliver (2008) for a brief case study on the U.S. Veterans Health Administration.
[c]We refer the reader to Sharfstein et al. (2018) for a short discussion on global budgets in Maryland.
[d]We refer the reader to NHS England (2018) for a review of the NHS Quality and Outcomes Framework pay-for-performance scheme.
[e]We refer the reader to James (2013) for a brief of the Medicare value-based HRRP.
[f]We refer the reader to Amgen (2017) for a news release regarding the agreement.
[g]We refer the reader to CMS (2017) for a fact sheet on the hospital value-based purchasing program.

3.2 Supply Chain Strategies in Action in Healthcare Supply Chains

SC strategies are the core of SCM. In deploying SC strategies, organizations need to consider their capabilities (e.g., capacity, flexibility, quality, speed), the features of the products and services they offer (e.g., functionality versus innovativeness), and the nature of supply and demand (e.g., volume, predictability). SC strategies should also align with the organizational strategy. For instance, healthcare entities whose mission is to increase access to care might pursue strategies that allow for economies of scale. There are numerous strategies used in SCM, such as integration, efficiency, responsiveness, process improvement, lean/six sigma, diversification, and outsourcing, and they are used to match demand and supply and to manage capacity, inventory, infrastructure, and so on. We proceed with a discussion of several SC strategies that are either commonly used in

or have a high potential to be applied to healthcare. We offer examples of organizations and systems that have successfully used these approaches to further their mission and goals, and we also highlight some of the challenges associated with certain strategies.

3.2.1 Coordination and Integration

Coordination refers to the organization of operations and processes of multiple interdependent entities, which enables effective joint work (Erhun and Keskinocak 2011). It is typically achieved when there are mechanisms in place that allow SC partners to consider each other's constraints, actions, and objectives in order to improve collective performance. Integration takes coordination one step further. In an integrated SC, connectivity between individual organizations is increased and silos are eliminated so that the SC operates as one cohesive entity. The level of integration may vary from loosely integrated, in which participating organizations have some degree of incentive alignment, to fully integrated, under which a firm owns and manages its own SC.

Information sharing can facilitate both coordination and integration. In the retail industry, the partnership between P&G and Walmart provides a notable example of how both firms used interorganizational information systems to their mutual benefit. Vendor managed inventory, a strategy that required Walmart to share its sales and inventory data with P&G, allowed P&G to make replenishment decisions for Walmart. This resulted in enhanced service levels and reduced inventories across the SC. Walmart's disclosure of point of sale data facilitated improved customer focus by permitting the partners to engage in better category management (Grean and Shaw 2002). In contrast, healthcare systems tend to be far less cohesive, which is in part, because many current policies and approaches addressing performance measurement and payment reform focus on individual providers (Fisher et al. 2007). Yet, such approaches that target specific entities rather than the system as a whole risk further reinforcing fragmented patient care and discouraging coordination across providers. The lack of coordination and integration between generalist and specialist medicine and the lack of integration among social care, healthcare, and mental health hamper health outcomes, patient experience, and continuity of care.

Researchers have made multiple efforts to improve coordination and integration in care delivery. At the strategic level, Groene and Garcia–Barbero (2001) models for integrated care. At the clinical level, Campbell et al. (1998) review the development of integrated care pathways for a specific clinical condition. Recently, two team–based patient–centered care models, the patient–centered medical home and perioperative surgical home, have been introduced with the goal of facilitating standardization, coordination, and transitions throughout the primary care continuum and the perioperative continuum, respectively (Hoff et al. 2012). ACOs are another possible solution to this challenge, as they integrate multiple healthcare organizations such as physicians' offices, hospitals, mental health services, and community and social care jointly into one unit. Designed as a population–level model, the underlying goal of an ACO is to improve the health of a given population by coordinating all of the population's healthcare needs, from birth to death.

While these integration initiatives focus on breaking down barriers and encouraging coordination between various healthcare providers and between healthcare and other services (e.g., community care), there is no one–size–fits–all model of integrated care. For developers of any initiative, it is critical to consider the context in which it will exist (i.e., different care settings and stakeholder perspectives) (Shaw et al. 2011). From a hSCM perspective, the particularity of context raises many interesting questions about capacity, scheduling, and contracting. For instance, within particular settings, one can consider: How can providers/services pool resources to ensure coordinated care? Which patients should flow across providers, and how and when should they do so? How should patient appointments be scheduled? A deep knowledge of the patient population is therefore necessary in order to reap the benefits of integration. Other key enablers of successful integration include rich data and an effective IT infrastructure, as well as standardized data collection protocols across organizations (Cox et al. 2016).

3.2.2 Standardization

Standardization, a process that ensures consistency across units, is another SC practice implemented in healthcare. Products, supplies, materials, equipment, processes, tasks, and services, among other things, can be subject to standardization, which yields multiple benefits.

Because standardization removes variability, it establishes consistent quality and increased productivity. Goods standardization can facilitate mass production that, in turn, can enable economies of scale. Furthermore, limiting the product selection can lower inventory costs. For instance, McDonald's achieves cost savings by offering the same menu of food items globally. In combination with careful adaptations to tailor products to local tastes, the company's consistent offerings have reinforced its brand image. Similarly, Southwest Airlines attains significant efficiencies through the use of a standardized fleet. Using a single type of aircraft has allowed the company to realize savings from training and maintenance costs and through its flexibility in scheduling (as both the fleet and the staff operating the aircraft are essentially interchangeable).

In healthcare, a leading example of a system that has improved quality and access to services while also lowering costs through standardized processes is Narayana Health, a chain of multispecialty hospitals in India. To enhance the efficiency of cardiac surgery, Narayana applies a production–line approach to surgical care, which relies on minutely detailed protocols for clinical tasks and on narrowly scoped task assignments to facilitate task downshifting by preventing dangerous errors (Erhun et al. 2019). Multiple surgeries can be performed consecutively because surgeons execute the tasks that only they are qualified to perform while, concurrently, other clinicians prepare the next patient for surgery. This allows surgeons to quickly move on to the next prepped patient (Taylor et al. 2017). At Narayana, each surgeon performs 400–600 procedures a year; the average U.S. surgeon performs 100–200 (Govindarajan and Ramamurti 2013, Erhun et al. 2019). This higher volume improves surgeon productivity and reduces costs. Another example of value obtained from standardized processes and specialization is Canada's Shouldice Hospital. For more than 70 years, this Ontario hospital has maintained a singular surgical focus on inguinal hernias. Although general surgeons do not perform more than 20 hernia surgeries a year, on average, Shouldice surgeons perform five to six surgeries a day (The Economist Intelligence Unit 2016). As a result of this hyper–specialization, the hospital has achieved a 99.5% success rate at a billing cost 50% less than other general hospitals in the province (The Economist Intelligence Unit 2016).

Healthcare providers have also relied on standardization in procurement. Standardized supplies and equipment lead to cost reductions stemming from volume discounts. Standardization in

purchasing also eliminates the extra time and effort needed to elicit, tailor, and cater to individual preferences. For example, Seattle Children's Hospital realized savings of 20% per case in supply costs after implementing standardized preference cards for laparoscopic appendectomy (Avansino et al. 2013).

3.2.3 Efficiency vs. Responsiveness

One popular SCM framework is Fisher's matrix (Fisher 1997), which ensures that the process used for supplying products (i.e., the SC type) is well suited to the products' characteristics: functional products require efficient SCs whereas innovative products require responsive SCs. For example, fast fashion necessitates a responsive SC. Zara, a champion in this regard, caters to rapidly changing demand through its highly agile SC, which incorporates information integration (i.e., constant feedback between stores and designers and daily analysis of sales and customer opinions) and delayed differentiation production processes (e.g., the purchase of undyed fabrics to be subsequently dyed according to color trends). Moreover, Zara can also accommodate demand for its functional products through its efficient SC practices that minimize cost; for example, consumer staples such as plain white t–shirts are produced in lower–cost markets with long lead times.

In healthcare, the pharmaceutical SC offers several examples of supply chain efficiency. Civica Rx, a hospital–led not–for–profit generic drug company, is a good example of an efficient SC. With the goal of decreasing costs and increasing availability of generic drugs, seven healthcare systems and about 500 U.S. hospitals have joined forces and committed to buying a fixed portion of their drug volumes from Civica Rx with a take–or–pay contract (Betz 2018). Civica Rx, in turn, has engaged in a long–term manufacturing and supply contract with Hikma, a contract manufacturer, to eliminate uncertainty in the generic drug supply and prevent drug shortages (Civica Rx 2019). Similarly, Healx, a U.K. biotechnology company, uses its proprietary artificial intelligence (AI)–based tool (Healnet) to identify and repurpose existing drugs to treat rare diseases (Kavadias et al. 2016), thus providing a faster and lower–cost approach to the discovery and development of rare disease treatments—an often–neglected segment of the industry.

Efficient care delivery is a hallmark of many world–renowned specialty healthcare facilities including Shouldice Hospital and Aravind Eye Care. Because these providers have a narrow surgical focus on routine procedures (inguinal hernias in the case of Shouldice and cataract surgeries in the case of Aravind), they can apply the principles of lean management and standardization to reduce costs. Conversely, nonspecialized general hospitals and hospitals' emergency departments are two examples of responsive care delivery. These facilities are designed to be flexible and agile in satisfying unpredictable demand (e.g., the diagnosis and treatment of complex patients with multiple comorbidities). It is possible for healthcare organizations to take advantage of both lean and agile strategies. For instance, leagile is a hybrid SC strategy that applies either a lean or an agile approach, as is most appropriate, to different stages of the SC (Agarwal et al. 2006). Hybrid strategies have also been used in a Swedish healthcare setting, where Aronsson et al. (2011) provide illustrative examples of how patient flow in a multi provider SC consisting of primary care, secondary care, and social services can be decomposed into several lean and agile subsystems.

A note of caution is in order when it comes to studying efficiency through hyper–specialization. Although hyper–specialization in operations may result in improved patient outcomes and decreased costs, it is not always the best model when viewed in light of a system. For one, healthcare is burdened with reimbursement distortions. As a result, and as discussed in Shactman (2005), specialty hospitals may *cherry pick* more profitable specialties and more profitable (i.e., less complex) patients. Conversely, general hospitals that pool services (Section 2.4) can use revenue from their profitable specialties to cross–subsidize the unprofitable services they are required to provide. Furthermore, general hospitals can cross–subsidize care for the poor and uninsured by catering to a variety of patients. Overall, service line design deserves further analysis, especially through the lens of supply chain thinking.

3.2.4 Pooling vs. Focused Operations

Pooling refers to the action of redesigning areas of the SC (by aggregating demand, resources, products, and capacity) to either reduce uncertainty or to hedge against uncertainty to mitigate its consequences (Cachon and Terwiesch 2009). Diminished demand variability allows for a lower

level of safety stock. Moreover, a consolidated product inventory decreases shortage and obsolescence risk. Thus, demand and product pooling enable better inventory management. Pooling can also result in cost savings. For instance, location pooling can reduce warehousing costs, whereas goods batching can lower transportation costs. Last, pooling can improve service: for example, to reduce customer wait times, some call centers pool call types rather than designating specific agents for specific customer call types.

There are many examples of pooling in different stages of the hSC. Consider, for example, procurement. At the hospital level, different specialties and departments may share the same procurement center for pharmaceuticals, supplies, and devices. Moreover, a growing number of hospitals engage in pooled procurement, routing their spending through intermediaries like group purchasing organizations. These intermediaries consolidate the purchase quantities of multiple hospitals to leverage larger purchasing volume, thus obtaining better prices than individual hospitals that purchase directly from manufacturers. In the vaccine market, UNICEF's Supply Division, the Pan American Health Organization, and the Gulf Cooperation Council Group Purchasing Program pool orders from low– and middle–income countries and procure products on their behalf (Bare 2015). Pooling is also used for production (e.g., the use of hospital labs, x–ray machines, magnetic resonance imaging machines, and operating rooms by different units/specialties), inventory (e.g., the use of the same warehouse by various departments of a hospital/s), and fulfillment (e.g., cross–provider use of a single, centralized appointment booking system). One emerging example of resource pooling is shared medical appointments, in which patients receive provider consultations in the presence of other patients with the same or a similar condition and which have been shown to improve outcomes and patient satisfaction while reducing waiting times and costs (Ramdas and Darzi 2017). Last, pooling is used in healthcare financing. A wide range of public and private agencies (such as national ministries of health, health insurance firms, and nongovernmental and community–based organizations) pool funding from various sources (such as taxes, insurance contributions, and external funding) to reimburse providers for individuals' healthcare (World Health Organization 2019).

As useful as pooling can be, it may not be an ideal strategy in certain situations. Studying operational performance within a hospital, Song et al. (2015) compare a pooled queuing system to

a dedicated queuing system. The authors find that a patient's average wait time and length of stay are longer when physicians are assigned patients under a pooled queuing system with a fairness constraint compared with a dedicated queuing system with the same fairness constraint. The question of pooled versus focused service lines therefore deserves further analysis with a simultaneous consideration of clinical, operational, and financial dimensions. Other recent inquiries into the uses and limitations of pooling include studies by KC and Terwiesch (2011), Christensen et al. (2017), Jiang and Sodhi (2019), Kuntz et al. (2019), and Freeman et al. (2020).

3.2.5 Incentive Mechanisms

The essence of a strategic orientation in SCM is aligning the intra– and interfirm goals and capabilities with those of the SC. Incentive mechanisms are financial or nonfinancial measures that encourage individuals (e.g., regulators, payers, hospitals, physicians, and patients) to undertake particular actions necessary for such an alignment. Disincentives and penalties, which deter individuals from performing certain actions, can also serve as alignment mechanisms.

In healthcare, to improve the distribution of human resources and match demand with supply, countries such as the United States and Canada have introduced incentive programs (student stipends and loan forgiveness, as well as compensation) to encourage physicians to train and work in underserved areas (i.e., rural or remote places) (Fedyanova 2018). Physicians can also be incentivized by nonfinancial means such as the use of internal transparency initiatives (e.g., letting colleagues see each other's performance data motivates them to improve patient experience; Lee 2015).

In addition to altering physician behavior, incentive mechanisms are used to promote healthy behaviors in individuals and to emphasize prevention. For instance, many employers and insurance companies (such as UnitedHealthcare and Kaiser Permanente) offer their employees and members various fitness and wellness programs, including discounts for gym memberships and activity trackers, as well as weight management, nutrition counseling, and tobacco cessation services.

At a higher level, incentive mechanisms can be used to encourage proper management actions. In traditional SCs, incentives are often used to induce information sharing to reduce or eliminate inefficiencies like the bullwhip effect. Similar approaches have been used in healthcare, where bed blocking, caused by a lack of available ward beds, is a common source of inefficiency and one of main drivers for overcrowding in emergency departments (Bretthauer et al. 2011). Nonemergency wards also often have bed blocking when elderly patients, although clinically ready to be discharged, continue to occupy hospital beds because community care and social care spaces are unavailable (Bottery et al. 2018). Bed blocking not only leads to resource misuse, but it can also prevent timely treatment. Incentivizing information sharing between upstream and downstream providers (e.g., between emergency departments and hospital wards and between hospitals and community care) can facilitate appropriate and advance planning that prevents or alleviates bed blocking. Another example of information sharing relates to hospital discharge summaries sent to patients' primary care physicians. Because poor communication threatens patient safety and continuity of care (Boddy 2019), improving the timeliness and accuracy of discharge summaries can help ensure that primary care physicians have the information they need when they need it. This can prevent the duplication of effort (such as repeated tests) and enhance patient care and patient and physician experience.

Reimbursement schemes are another example of incentive mechanisms that have been used to induce appropriate treatment behavior from providers. Pay–for–performance (P4P) is a payment model that encourages healthcare providers to meet certain performance measures through the use of financial (dis) incentives (Table 3). One notable example of P4P is the Hospital Readmissions Reduction Program (HRRP), which was implemented by the Centers for Medicare and Medicaid Services in 2002 to further the national goal of improving healthcare by linking payment to quality of care (Joynt et al. 2016). Under HRRP, hospitals with excess 30–day readmissions face payment penalties of up to 3%. The program has generated debate surrounding the extent to which it reduces readmissions: Zuckerman et al. (2016) find readmission trends consistent with hospitals responding to incentives, Zhang et al. (2016) show that HRRP's benchmarking mechanism can lead to an increase in the number of non–incentivized hospitals (which opt to pay penalties rather than reducing readmissions), and Ody et al. (2019) argue that HRRP has had no effect on readmission reduction or that its effect has been overstated. Chen and Savva (2018) suggest that

the reduction in readmissions attributed to HRRP may be caused in part by higher observation bed use, whereas Wadhera et al. (2018) find HRRP to be associated with post discharge mortality among patients hospitalized for heart failure and pneumonia. Andritsos and Tang (2018) show that P4P (i.e., HRRP) is more effective than fee–for–service (FFS) or bundled payment in reducing readmissions when patients' efforts are considered using a coproduction model.

Another performance metric commonly targeted and investigated by regulators and researchers is patient wait times, which may result in diminished health outcomes when they are too long. Patients may also endure other, often overlooked, consequences such as wages forgone while waiting for treatment and decreased quality of life because of increased pain and suffering (Barua et al. 2018). In their study within a public healthcare system, Guo et al. (2019) examine the impact of the reimbursement policy on social welfare, the revisit rate, and wait times. They show that when the patient pool is large, a bundled payment scheme dominates an FFS scheme in terms of higher social welfare and a lower revisit rate, but the FFS scheme prevails in terms of a shorter wait time. However, in a less–congested system, the bundled payment scheme outperforms the FFS scheme in all three measures. In a different setting, one where regulators are interested in incentivizing both cost and wait time reduction, Savva et al. (2019) examine yardstick competition in the hospital industry. The authors present a scheme that modifies the transfer payment of the standard cost–based yardstick competition, and they show that if the regulator has prior knowledge of providers' average wait times, the scheme can significantly improve system efficiency.

These examples demonstrate how incentive mechanisms can be used to change individual and institutional behavior to improve patient outcomes and experience, as well as provider performance. However, well–intentioned incentive mechanisms sometimes result in perverse incentives and unintended consequences (as the debate on the effectiveness of HRRP demonstrates). Thus, stakeholders (such as policy makers) should take great care to preempt any ramifications for the hSC whenever they introduce new incentive mechanisms, as well as to evaluate, assess, and amend existing mechanisms.

3.3 Redesign of Healthcare Supply Chains Using New Care Models

Numerous care models have recently been introduced in various national and regional healthcare systems. In this section, we discuss three notable trends that shift care from treatment to prevention, from hospitals and clinics to primary care and patients' homes, and from broad treatment approaches to personalized/precision medicine. These trends build on all three dimensions of hSCM. They reinforce the customer focus as they attempt to maximize patients' overall health and quality of life and enhance treatment outcomes. In combination with new health innovations such as digital health, AI, and blockchain (Table 3.4), these changes are reinventing care delivery through a systems approach by becoming key drivers of integrated care models, such as ACOs and value–based healthcare. Finally, through recently introduced reimbursement schemes (Table 3.3), these new trends aim to align the shifting goals and priorities of stakeholders.

Table 3.4. Clinical and public health, operational, and financial challenges in hSCs.

Technology	Role	Benefits	Challenges	Opportunities
EHRs	Decreased reliance on paper medical records	Availability of timely, more accurate, complete, and legible documentation that can be shared with patients and other clinicians[a]	Interoperability	Standardization of records Customization accounting for the needs of individual providers
Telemedicine	Remote delivery of healthcare services	Increased access to underserved communities by overcoming geographical barriers[b] Affordability Improved health outcomes and quality[c]	Reliability Resistance to change	Properly devised incentive mechanisms and reimbursement to bolster uptake
Wearable technology	Measurement and collection of data on users' wellness, fitness, and health information	More emphasis on self-care by enabling users to track and monitor health data Support for healthier behavior (e.g., getting more sleep and exercise) Engaging patients in proactively seeking medical attention based on indications from wearables Reduced burden of monitoring[d] Remote monitoring by physicians to facilitate prediction and prevention of certain health conditions (e.g., hypertension)	Data security	Data generation for quantitative analysis in order to improve care and data-driven decision-making and to assist in medical advancements
Personalized medicine	Clinical interventions tailored to individual patient characteristics	More successful outcomes through an analysis of which treatments will be most effective for which patients by factoring in individuals' differences in genes, demographics, and lifestyle	Complexity[e] Cost (typically more expensive than conventional approaches)	Processes to best gather, interpret, and use data Value[f] assessment of personalized medicine to drive widespread adoption
Online healthcare platforms	Forming communities of patients, professionals, or both, using information and communication technologies such as blogs, chats, and forums	Online knowledge transfer within and among professional networks (in comparison with traditional in-person encounters such as medical conferences)[g] Communication across professionals caring for complex patients Improved patient-centered care via information sharing More knowledgeable, supported, and empowered patients, resulting in more active self-management[h]	Accuracy of information	Improved digital health literacy for individuals, with a particular focus on assessment of information

Table 3.4 (Continued)

Technology	Role	Benefits	Challenges	Opportunities
Blockchain systems	Secure storage and distribution of pharmaceutical, clinical, patient, and billing data in distributed networks	Better health data management allowing all pertinent providers to have access to a patient's complete medical history[i] Drug development based on patient data[j] Mitigation of prescription fraud,[k] drug counterfeiting,[l] and claims and billing fraud[m] Elimination of intermediaries for health information exchanges, improving SC efficiency	Lack of infrastructure and competency	Regulatory and academic support

[a]The Office of the National Coordinator for Health Information Technology (2019).
[b]World Health Organization (2009).
[c]For instance, the tele-ICU acts as a second set of eyes and allows for additional clinical support and surveillance with the intent of improving patient safety and outcomes (Goran 2010).
[d]For example, the insertion of a continuous glucose monitor allows for glucose monitoring throughout the day and night while reducing the number of finger-pricked checks needed.
[e]Expansion in decision algorithms and treatment options from increasing availability of information (Jameson and Longo 2015a).
[f]Personalized medicine can also decrease costs; for example preventing hospitalizations resulting from adverse drug reactions.
[g]Readers are referred to van der Eijk et al. (2013) for a discussion on the four benefits of OHCs.
[h]Wicks et al. (2011) show respondents, part of an epilepsy OHC, reported benefits such as forming relationships with other patients, gaining a better understanding seizures and treatments.
[i]Readers are referred to Mettler (2016) and Marr (2017). See also Gem Health Network and MedRec for two such initiatives.
[j]See HealthBank for an example of a data-trading platform.
[k,l,m]Readers are referred to Engelhardt (2017), del Castillo (2016), and Marr (2017), respectively.

3.3.1 Shifting the Focus of Care from Treatment to Prevention

Globally, one in three adults lives with more than one chronic condition (Hajat and Stein 2018), such as arthritis, diabetes, and mental illness. Chronic diseases deteriorate individuals' health, reduce life expectancy, and degrade quality of life. Care for the chronically ill is also costly; in the United States, chronic disease accounts for nearly 75% of aggregate healthcare spending (Raghupathi and Raghupathi 2018). Prevention is gaining traction as an essential measure in tackling this burden.

Bauer et al. (2014) describe the strategies employed by the Centers for Disease Control and Prevention (CDC) to reduce the preventable burden of chronic disease: (1) epidemiology and surveillance to monitor trends and inform programs; (2) environmental approaches that promote health and support healthy behaviors (e.g., zoning regulations that encourage walking and cycling); (3) health system interventions to improve the effective use of clinical and other preventive services (e.g., improvements in controlling high blood pressure); and (4) community resources linked to clinical services that sustain improved management of chronic conditions.

Several remarks are in order concerning these strategies. First, in addition to facilitating epidemiology and public health surveillance, data emerging from new health information technologies can be combined with advanced analytical methodologies such as econometrics and machine learning algorithms to assess the effectiveness and efficiency of newly established care and prevention models (Moore et al. 2010, Perreault et al. 2010).

Second, a vast array of organizations is naturally involved in the design and delivery of various laws, policies and environmental approaches, including governments, employers, the private and voluntary sectors, and the media, as well as health, community, and social care entities (Alderwick et al. 2015, Lovell and Bibby 2018). Supply chain thinking suggests that, to further the goal of reducing the occurrence of chronic disease, these entities need to engage in stronger collaboration (i.e., a systems approach) driven by the overarching goal of enhancing prevention (i.e., a strategic orientation). As such, process redesign may enable improvements in care delivery. For example,

Thompson et al. (2018) introduce the notion of temporal displacement of care and show that the use of information technology and analytics can lead to value creation in the hSC (better clinical outcomes and lower cost) when early, preventive services displace later–stage, high–cost interventions for the chronically ill.

Last, relating to CDC strategies (3) and (4), it has been argued that, because general practitioners have accumulated knowledge of and established rapport with individual patients and their families, general practice is in a unique position to play a proactive role in emphasizing prevention and improving population health (Thorlby 2013; see, for example, the Gesundes Kinzigtal model in Germany, Hildebrandt et al. 2010). This suggests that a shift from treatment to prevention may need to coincide with a shift from secondary care (e.g., hospitals and clinics) to primary care (e.g., general practices) and care at home, which we discuss in the following section.

3.3.2 Shifting Care Closer to Patients' Homes

The second emerging trend in handling the prevalence of chronic disease is that the site of care is moving closer to patients' homes. Aside from potential cost advantages, this shift may offer improvements in the quality of care and patient experience. One model that incorporates such change is the primary and acute care system (PACS), which was recently proposed by the NHS and which aims to move care out of the hospital through the formation of a single entity responsible for delivering the full range of primary, community, mental health, and hospital services. Built on principles of patient–centricity and integrated care, PACS is a noteworthy example of supply chain thinking in healthcare. In terms of how such integrated care models should be developed, Collins (2016) points to the importance of defining how the proposed model will be governed, the organizational form it will take, and how risks will be shared.

The localization of care may also be aided by technologies such as telemedicine, wearable devices that facilitate remote monitoring, and online platforms that allow some types of care to take place in patients' homes. Examples of organizations adopting such technologies include Onduo, a Verily–Sanofi joint venture providing diabetes patients with tools, coaching, and clinical support through a virtual care program; Roche's mySugr, which enables patient centered digital diabetes

management; and 111.inc, a Chinese platform that provides online consultations and e–prescription services through a network of medical professionals, as well as online pharmacy services for retail and business customers. Online health communities (OHCs), such as PatientsLikeMe, bring together groups of patients, professionals, or a mixture of both using communication technologies like blogs, chats, and forums. Accessible primary care (e.g., general practitioners and pharmacists) and afterhours services (e.g., NHS 111, an online/telephone service for urgent medical problems), can serve as alternatives to hospitalization. Organizational processes can also enable self–care. An internationally recognized community care model, the Buurtzorg model of care, uses teams of nurses who are responsible for a few dozen patients in a particular area, promoting continuity of care. Nurses act as health coaches by training patients and their families in self-care and by emphasizing preventive health measures (Brindle 2017).

In addition to a rising chronic disease burden, the growing and aging population poses a major challenge. Worldwide, the population aged 65 and over is increasing faster than any other age group (United Nations 2019). Typically, elderly patients have a number of interrelated chronic health and social issues. Although a shift to prevention and to providing care closer to home may make significant strides in addressing these issues, “medicines and care pathways have been designed based on evidence from large populations and, although clinicians do their best to tailor this to the needs of individuals, we still have a broad–spectrum approach to treatment” (Roche 2018, p. 2). The clash between this broad–spectrum approach and complex patient conditions points to the necessity of considering patients’ unique characteristics and needs, which leads us to personalized medicine.

3.3.3 Shifting from Broad Treatment to Personalized/Precision Medicine

Personalized medicine is a broad term that refers to a departure from one–size–fits–all, population–based strategies to tailored interventions centered on individuals. The narrower term precision medicine is typically used to refer to treatments targeted to the needs of individual patients on the basis of –omics (e.g., genomics, proteomics) data (Ayer and Chen 2018). Personalized medicine promises more successful outcomes through determining which treatments will be most effective

for which patients by factoring in individual differences in genes, demographics, and lifestyle (Jameson and Longo 2015a, b), as well as through improved patient assessment, diagnosis, and prognosis (Hamburg and Collin 2010). Moreover, with the use of diagnostic technologies, personalized medicine can play a role in prevention by detecting ill health before symptoms appear, paving the way for preventive interventions that are similarly personalized.

One SC strategy that may grow in importance for healthcare is mass customization,[2] which combines flexibility (allowing firms to provide customers with individualized, custom–made products and services) with low unit costs achieved through mass production (Minvielle 2018). Mass customization will allow healthcare organizations to respond to both the growing number of chronically ill patients who require a sophisticated combination of long–term care and to patients who are becoming more vocal in expressing their demands, preferences, and expectations. Such a strategy would facilitate increased attention to patient centric care (that seeks to treat the patient rather than the disease) and the growing focus on improving the quality of care and patient experience. Mass customization can lead to quality improvement by enhancing outcomes and patient satisfaction (e.g., through tailoring clinical decision making to individuals' needs). Furthermore, identification of the most appropriate treatment, in addition to personalized follow up and better patient adherence, can lead to cost savings from unnecessary treatments/actions.

Another fundamental aspect of customized care, one which has also been facilitated by advances in technology, is categorizing patients. Healthcare organizations and researchers can now segment large patient populations into smaller groups based on characteristics such as genetic profile (Gandhi et al. 2013). Moreover, Volpp et al. (2018) note that defining behavioral phenotypes and expressed patterns of behaviors (from clinical data and everyday monitoring via wearable devices and social media footprints) can give providers a systematic approach to identify which patients

[2] Mass customization has been used in various industries including auto manufacturing (customers can choose vehicle attributes such as the engine size and interior), apparel (products come in various patterns and colors), and the PC industry (the most well–known example being Dell, where customers can select the desired processor, storage, etc.). Minvielle et al. (2014) develop a framework for managing customization in healthcare. On a broad level, the key factors of the framework relate to categorizing patients, the technical and human factors in the service delivery (i.e., ensuring the necessary IT, developing provider service skills, and improving patient self–management) and assessment (i.e., whether the service met patients' needs and was financially sustainable).

to target for which interventions. The authors suggest that such improved patient targeting can help the healthcare sector derive more value from currently available treatments instead of spending more to develop new medical technologies. For instance, behavioral, social, and environmental data can be used to determine approaches that facilitate better adherence to existing efficacious treatments. AI is another technology that is being used to successfully apply and advance personalized medicine, with the NHS being one case in point. The U.K. government has announced plans to allocate £250 million for a national AI laboratory, in addition to offering five million people a free personalized health report based on their DNA (Neville 2019). For more information on the application of AI, we refer readers to a recent Roche report outlining a long–term framework of how advances in digital technologies, genomic profiling, and machine learning can revolutionize personalized healthcare from the patient journey to wider population health (Roche 2018); to Roden et al. (2008), who developed a deidentified DNA biobank linked to an electronic medical record system with the intent of discovering genotype–phenotype relationships that can enable personalized medicine; and to Yu et al. (2016), who use machine–learning methods to predict the prognosis of lung cancer patients, thereby advancing precision oncology.

3.4 Research Opportunities and Concluding Remarks

It is our hope that this paper provides readers with a better understanding and appreciation of the importance of hSCM, which we broadly define as the management of people, processes, information, and finances to deliver medical products and services to consumers. As described in Table 3.2, a number of factors, including information asymmetries, ambiguous and disparate valuations of healthcare, lack of accurate costing information, perverse incentives resulting from payment structures, and siloed services, make the adoption of hSCM an onerous task. Although healthcare systems can make strides in improving their operations through applying the various lessons learned over decades of SCM and supply chain thinking, hSCM will only yield significant value if tools, strategies, and approaches are tailored or created to address the challenges and opportunities unique to healthcare.

Integration is key for healthcare moving forward, both within the healthcare sector and across social and community care and public health. These sectors impact one another; for example, the

healthcare sector faces delayed transfers of care because of inadequate community care, individuals with unmet social needs may end up relying more heavily on primary and secondary care, and all sectors exert *gravitational pull* on each other's workforce. Models that address these issues through integration and collaboration should be a topic of interest for practitioners and researchers, who may ask questions like: What is smart integration? From a systems perspective, which providers should provide which services, and when? Consequently, how should their processes be aligned? How can information technologies (such as the flagging systems used in Toronto's Mount Sinai Hospital, which allow primary care, home care, emergency, and inpatient care providers to effectively communicate geriatrics patients' needs; Mount Sinai Hospital 2016) improve interprofessional, collaborative care for complex patients? Should providers be incentivized and rewarded for collaboration? If so, how should the risks and benefits be shared? At a higher level, how should primary, secondary, tertiary, community, and social care organizations be reorganized, individually and collectively? In addition to engaging with these questions, any potential healthcare model needs to incorporate the impact of behavioral aspects such as patient engagement and provider receptiveness of patient preferences on the clinical, operational, and financial dimensions of care.

One key point we can take away from this overview of supply chain thinking in healthcare is that a better understanding of the value of preventive models closer to home is essential for healthcare delivery. More evidence quantifying the spillover and longitudinal effects of public health initiatives is needed to address the investment challenge for prevention discussed in Table 3.2. For insights into this new area of research, we refer the reader to Marshall et al. (2018) for a description of The Social and Economic Value of Health research program funded by the Health Foundation, which will examine the complex, multidirectional relationship between individual health and socioeconomic factors using innovative statistical methods and varied data sources (notably, genetic data). In addition, the cost impacts, workforce consequences, and the social impacts on patients and carers resulting from the reorganization of care delivery should be studied. Such redesign also raises other questions. How can we use online, reliable resources and telemedicine to enable easy access to care? How can we carefully integrate these resources with more traditional care delivery methods while avoiding unintended consequences? (For instance, Bavafa et al. 2018 show that e–visits trigger more primary care office visits, which come at the expense of fewer new

patients accepted by physicians.) How can we design incentive mechanisms and payments (such as the Gesundes Kinzigtal model) that encourage early prevention rather than remaining passive until treatment is necessary? Such shifts in care require identifying susceptible patients early on; therefore, how can we use data and predictive modeling as an integral part of the design of care delivery models?

The proliferation of EHRs, health technologies, and online healthcare platforms have generated large amounts of data. The surge in data availability, in conjunction with growing computer power, has allowed healthcare analytics tools, such as AI and machine learning, to play an expanding role in the advancement of healthcare. For example, machine learning is now used to inform diagnosis (Miotto et al. 2018), make predictions (Finlay 2018), develop prescriptive treatment algorithms (Jameson and Longo 2015a, Champagne et al. 2018), reduce readmissions (Liu et al. 2018, Queenan et al. 2019), and objectively evaluate physicians (Foster et al. 2018) (see Guha and Kumar 2018 for an overview of how big data analytics has been applied in the healthcare domain and for a roadmap of future research). Moreover, health information exchanges, facilitated by technologies like blockchain (Babich and Hilary 2020), may lead to more efficient hSCs by minimizing transaction costs and wastes (e.g., fraud, counterfeits).

There are, however, concerns regarding the accuracy and security of data, as well as the feasibility, cost, interoperability, and operational complexity of new ITs. Complexity can also hinder the adoption of various trends in healthcare, such as personalized/ precision medicine. Moreover, as the availability of data and healthcare analytics capabilities both increase, hSC members (such as clinicians) are faced with an expansion in decision algorithms (e.g., treatment options) (Jameson and Longo 2015a), which amplifies the uncertainty challenge facing healthcare. To manage this complexity, stakeholders will need to establish best practices for gathering, interpreting, and utilizing data. Improving data interpretability, in particular, can facilitate the development of effective strategies for managing uncertainty. Therefore, we encourage researchers to consider questions such as: How can stakeholders make use of data to advance health; which methodologies, tools, and data should be applied, and to which contexts? Which stakeholders, and what actions, play a role in ensuring data protection? (For example, should patients own and control their own health data and records?) How can data be optimally integrated across systems

and stakeholders in the hSC and which processes need to be put in place to establish this? How can we best enable adoption of new technologies and approaches and overcome resistance to change? Accordingly, how can the value that new technologies create for hSCs be determined, measured, and shared?

In this paper, we have taken a high–level view to discuss how supply chain thinking (Figure 3.1) provides an opportunity for healthcare to understand, evaluate, and improve its complicated and often inefficient ecosystem. A more focused view of hSCs may lead to opportunities to adapt or develop SC frameworks from other domains for the healthcare context. For example, frameworks such as the supply chain operations references (SCOR) model may be adapted to concentrate on the evaluation of particular hSCs, such as pharmaceutical SCs. Additionally, in Tables 3.3 and 3.4, we present many challenges and opportunities for payment mechanisms and healthcare technologies, respectively, and in an appendix, we offer a categorization of hSCs and a synopsis of research for each hSC subcategory. The challenges, opportunities, and references we provide may spur potential ideas for future research.

The complexities and inefficiencies found in hSCs put hSCM in a leading position to improve the provision of healthcare. It is only when an improvement initiative concurrently satisfies the clinical, operational, and financial dimensions that we expect to see hSCM offer considerable value. Meeting this requirement may prove to be a rewarding (but by no means easy) feat, making hSCM a promising field for researchers, practitioners, and policy makers. We believe that the complexity in managing hSCs offers opportunities for important and impactful research avenues involving key SC strategies such as coordination and integration (e.g., new care models), mass customization (e.g., the rise in precision medicine), and incentives (e.g., emerging reimbursement schemes).

“There is a change in the air,” Roy Lilley wrote in his popular healthcare blog nhsManagers.net on September 10, 2019. He offers a slightly cautious take on how SCM can be used in healthcare, emphasizing the extraordinarily complex and challenging environment of care delivery. We believe that the hSCM framework described in this paper can contribute to the future success of healthcare delivery. More importantly, new research in line with supply chain thinking will

advance healthcare management and expose research opportunities, which might not only help address inefficiencies we observe in healthcare delivery but also provide insights relevant to traditional SCs.

3.5 Epilogue: COVID–19 Pandemic and Healthcare Supply Chains

As we were wrapping up this paper, global SCs,[3] including healthcare SCs, have been thrown into disarray and scrutiny by an infectious respiratory disease called COVID–19. The disease, which is believed to have started in Wuhan (China) in November 2019, has quickly spread to other parts of the world and was declared a pandemic by the World Health Organization on March 11, 2020. Countries around the world have responded to the disease with varying degrees of actions, ranging from social distancing to quarantines and lockdowns. As of April 25, more than 2.9 million cases have been reported across the world, with more than 202,500 resulting in death (https://www.worldometers.info/coronavirus/).

There are still a lot of unknowns about the origin, progression, infectivity, and treatment of the disease, as well as what the next 12–18 months will bring. Vaccinations against the disease are currently under development, but none are yet approved, and it may take many months for a vaccine to be rolled out to market.

Despite earlier epidemics, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza, as well as various calls over the years regarding the possibility and the crippling impact of such a future pandemic, global hSCs were

[3] The occurrence of global SC disruptions and failures is not new. For example, the 2011 Tohoku earthquake and the tsunami that followed disrupted semiconductor, high–technology, and automotive SCs, in some cases leading to plant closures of up to six months. Geographical concentration of SCs made it challenging for many semiconductor companies to cope with the disruption (Schorpp et al. 2020). When Boeing launched the production of its 787 Dreamliner in 2007, the company promised to do it in record time. However, Boeing's issues in managing their SC led to a launch delayed by a number of years (Tang et al. 2009). In 1995, Apple faced high customer interest for its new Power Macs but could not satisfy demand because of limited inventory, which ultimately resulted in an order backlog reaching $1 billion at one point. As a result of deploying the incorrect SC strategy, Apple lost its market position (Digest SC 2006). Healthcare executives should therefore be aware of such deficiencies in SCM, which provide significant learning opportunities to curtail the potential of falling into similar pitfalls.

caught underprepared by the COVID–19 pandemic. COVID–19 created a surge demand in medical SCs, increasing the need for infrastructure (e.g., hospital beds, intensive care unit (ICU) beds, and ventilators), workforce (e.g., doctors, nurses, and carers), and supplies (e.g., oxygen). National and regional health systems are competing for limited resources such as face masks, medications, personal protective equipment (PPE), medical equipment, and test kits. On the supply side, global SCs are experiencing difficulties in the production and distribution of such items, with delivery times growing longer (Bloomberg 2020). Despite some countries relaxing their restrictions, production facilities are not working at full capacity. Transportation disruptions complicate the delivery of products across regions and countries. Worse still, competition for logistics is exacerbated by many people now relying on online shopping because of movement restrictions. Shortages are further complicated by national and international regulations on PPE and test kits. For instance, many suppliers and buyers are waiting for national (such as FDA) and international (such as Conformité Européenne) certification for newly developed products so that they may be able to produce and distribute them.

To create much needed capacity, governments and healthcare organizations have been learning from each other to develop and promote prevention strategies that *flatten the curve*, that is, reduce the speed of disease spread (Cyranoski 2020, Mattiuzzi and Lippi 2020) while researchers have sprung into action to develop models to support intervention decisions (Imperial College London 2020, Kaplan 2020). In the United Kingdom, the NHS quickly reacted to the increase and anticipated increase in demand by undertaking multiple measures, such as canceling nonurgent surgeries and discharging all hospital in–patients who were medically fit to leave (NHS England and NHS Improvement 2020). The government called out to car manufacturers to produce at least 20,000 ventilators. With ventilators, regular patient beds can be repurposed so that patients can receive respiratory support outside of ICUs (e.g., hospital wards or even nursing homes). In order to increase the capacity of medical staff and better control for the potential workforce reduction because of COVID–19 infections (especially given the lack of sufficient and quality PPE), recently retired professionals were called back to work, and some final year medical students have been allowed early registration so that they can join the hospital workforce. Strategies for the sourcing of PPE for health personnel warrants mention. A call by the *Journal of the American Medical Association* for ideas addressing the impending PPE shortage received more than 100,000 views

and generated more than 250 comments. Livingston et al. (2020) summarize the proposed strategies that include the reuse of PPE, importing PPE from international suppliers, reclaiming PPE from other industries, repurposing items into PPE, rationing the allocation via regional coordination, reducing patient contact through various measures, and canceling nonessential services that require PPE, among many others.

Despite these reactive actions, there were also several missteps in the early phases of the pandemic. The number of infections and deaths in many countries could have been scaled down through appropriate interventions such as broad testing of symptomatic and asymptomatic populations, better contact tracing and isolation of susceptible patients, earlier social distancing and lockdown measures, protecting health professionals through access to PPE, increased coordination between healthcare delivery, public health, community care, and social care; and by coordinating and commencing planning and procurement activities much earlier. These steps would have shifted the focus from treatment to prevention and would have more effectively flattened the curve. In a sense, hSCs had a common ailment of traditional SCs, where managers are more successful in their reactive planning rather than their proactive planning. Careful planning reduces the need for dire reactive actions. For example, measures such as calling retired healthcare workers back to the workforce have been met with both praise and some criticism. With proper planning, the course of action would have been more effective if returning workers were ensured adequate PPE. The need for former workers could have been curtailed had there been proper and timely workforce planning.

However, as is the case with any major disruption, COVID–19 has created opportunities for innovation in hSCs and has started to advance the adoption of new care models discussed in Section 3.3. Given the difficulty of controlling the disease without effective treatments and a vaccine, pharmaceutical and biotech companies have ramped up development efforts. Universities and research laboratories are using technologies, such as three–dimensional printing and AI, to help produce supplies and assist in triage and supply allocation decisions, while companies have used users' location data to shed light on responses to policies. The pandemic is triggering and accelerating the implementation of telemedicine, which not only brings treatment and care closer to patients' homes but also increases service efficiency by pooling remote resources. Moreover,

telemedicine safeguards patients and medical staff from infection. In the United Kingdom, more than 80% of primary care patients are now being managed through digital care. Researchers have already started thinking about how AI can be used to measure "an individual's clinical risk of suffering severe outcomes" to guide personalized care and resource allocation, if not for COVID–19, for future pandemics (Evgeniou et al. 2020).

The COVID–19 pandemic has reminded us of the importance of being adaptive in our approach in the application of supply chain thinking and provides many opportunities for the future of hSCM. As health systems around the world emerge from the pandemic, hSCs will need to consider the follow–on consequences such as the toll on mental health (in particular, that of frontline workers) and effects of cancellations to nonessential services. The COVID–19 crisis calls for the formulation of long–term contingency plans and supply chain thinking in hSCs.

3.6 A Reflection

Following the publication of the paper that Chapter 3 is based on, I continued to consider how SC thinking applies to healthcare, especially in light of recent developments such as the COVID-19 pandemic. Sparked by a conversation with prominent HOM scholars[1], I contemplated the value of hSCM, reflecting on questions such as 1) how is healthcare *supply chain* management different from healthcare management? 2) how can SCM and OM researchers contribute to making impactful changes to hSCs? And 3) How can improvement initiatives be successfully implemented and sustained in hSCs? This subchapter aims to shed light on these important questions.

The popularity of "supply chains" and "supply chain management" skyrocketed during the COVID-19 pandemic as a result of the many crises that shook global SCs. More and more companies and individuals looked towards traditional SC concepts and solutions to address challenges faced in their businesses. While the increased awareness in SC thinking bolsters the interest in and the audience of our research, it also runs the risk of reinforcing the usual procurement– and logistic–focused definition of SCM. Chapter 3 adopts a broader definition of

[1] This subchapter reflecting on the ideas in "Supply Chain Thinking in Healthcare: Lessons and Outlook" was written based on an interesting discussion with Professor Stefan Scholtes and Professor Tinglong Dai. I thank them for their suggestions and insights which are conveyed in this subchapter.

hSCM as *the management of people, processes, information, and finances to deliver medical products and services to consumers, with the aim of improving clinical outcomes and patient and provider experience, while controlling costs* (Berwick et al. 2008, de Vries and Huijsman 2011). In doing so, the research extends SC thinking beyond a prevailing view centered around the procurement and logistics of healthcare supplies and services. While stepping outside of the traditional boundary of the discipline, the definition admittedly falls short of being precise and informative. This definition bares resemblance to a more general definition of "healthcare management" which is "the practice of providing leadership, management, and direction to organisations that provide healthcare services and to different units within those organisations and is centered on three main concepts: effectiveness, efficiency, and equity*"* (EHMA 2023).

During our discussion, we converged towards a more informative view of hSCM. As echoed throughout the dissertation, healthcare is a complex system. Thus, SC thinking[2] in healthcare is a *way to decomplexify the healthcare system so that it can be managed*. Consequently, a hSC is a *subsystem of the broader, more complex, healthcare system and can be manageable if the following two characteristics hold: (a) it is sufficiently simple so that it can be optimized as a subsystem (in other words, a standalone SC), and (b) this optimization does not create spillovers to the remaining system.*

To illustrate the revised definition, the subsequent paragraphs discuss the drivers of complexity in healthcare and the various impetuses for change in healthcare systems. Pertaining to the first characteristic of the definition, the role of modelling research in optimizing hSCs is discussed. Relating to the second characteristic, the importance of empirical analysis in evaluating spillovers

[2] SC thinking differs from systems thinking as systems thinking is only one aspect of SCM. Systems thinking comes into play in that SCM as a philosophy considers all the entities in a SC as one integrated system. SCM, however, is further characterized by a customer orientation, i.e., the activities of the SC are focused on creating value for the customer. SCM is also characterized by a strategic orientation, i.e., the goals and capabilities of all the entities in the SC should be aligned to the goals of the overall chain to create value, or "expand the pie", and avoid wastes and inefficiencies in the chain (Mentzer et al. 2001). In other words, a strategic orientation helps to coordinate the SC. As previously discussed, *healthcare* SCM combines SC thinking with a simultaneous consideration of clinical, operational, and financial dimensions.

is also considered. Finally, the subchapter discusses how hSCM can be used to create impactful as well as sustainable improvements in hSCs.

What makes healthcare so complex?

Healthcare is an inherently complex system. “No other industry or sector has the equivalent range and breadth—such intricate funding models, the multiple moving parts, the complicated clients with diverse needs, and so many options and interventions for any one person’s needs. The various combinations of care, activities, events, interactions, and outcomes are, for all intents and purposes, infinite” (Braithwaite 2018). Chapter 1 of the dissertation discusses some of the issues that contribute to the difficulty of managing healthcare systems. Readers are referred to Section 1.1 for an overview. However, several factors are reiterated and further introduced as drivers of complexity in the healthcare system.

The healthcare system is comprised of many components such as staff, patients, finances, information, goods, and services, etc. Due to the large number of these elements and a degree of *unpredictability of their interactions*, the behavior of the healthcare system is hard to predict and therefore difficult to manage (Braithwaite 2018). There is a wide range of stakeholders across the different hSCs (Table 3.1), each with their own attributes, goals, constraints, and risks, which play a unique but interrelated role.

Stakeholder actions are guided by different *incentives*. “Health professionals, for example, focus on payment for services and autonomy. Care facilities seek high-margin services and low supply costs. Suppliers focus on intellectual property protection and volume. Meanwhile, consumers seek accessible services and low out-of-pocket costs. Payers pursue the right to select risk and limit cost. Purchasers want more value at the lowest cost” (Grossmann et al. 2011). Even between the same type of stakeholder, incentives can be vastly different due to various considerations. For instance, “Medicare, whose relationships with its enrollees sometimes last decades, may see far more value in an innovation with a long-term cost impact, such as an obesity reduction treatment or an expensive diagnostic test, than would a commercial insurer, which typically sees an annual 20% turnover” (Herzlinger 2006), influencing their willingness to pay for healthcare interventions.

Misaligned incentives can give rise to various inefficiencies and wastes in the SC (refer to Section 3.2.5), and cause stakeholder to take part in a zero-sum game (Porter and Teisberg 2006), stifling value creation.

Stakeholders also compete for *limited resources* and *resources may be shared/pooled* between different individuals, units, or organizations. This adds to the complexity as it can lead to issues such as gaming, strategic behavior, and ineffective and/or inefficient redeployment of existing resources. Aside from differing incentives and agendas, stakeholders also *differ in their power and ability to influence decisions* and public policy and opinion (Herzlinger 2006). Not surprisingly, there are *trust issues* across stakeholders (e.g., even though patients trust their own physicians, they distrust the "system" (Norris 2007)).

Moreover, stakeholders are *guided and constrained by different boundaries* such as the rules, procedures, and policies set forth by their organizations, regulators, and local context. This may explain why the replication of improvement initiatives sometimes fail when repeated across seemingly comparable entities. In such cases, although the inputs (e.g., staff, equipment, etc.) are the same or similar between systems, the systems may respond in very different ways (Braithwaite 2018).

As discussed extensively in Section 3.B.3, the *funding* and *reimbursement* of healthcare goods and services also adds a substantial layer of complexity. Questions such as the following make the management of SCs taxing: Who will pay for a healthcare product's research and development? Who will pay for its use and how much will be paid? (Herzlinger 2006), What incentives and disincentives do the various payment mechanisms carry for stakeholders (refer to Table 3.3)? Does the reimbursement reflect the true value of the service provided?

Lastly, the healthcare system is *adaptive* in that *its behavior changes over time.* That is, the system cannot be completely understood by knowing its individual components (Braithwaite 2018). For instance, with the advancement of technology, the management of healthcare systems must be forward looking. Consider, for example, the rollout of the polio vaccine which completely

eliminated entire healthcare subsystems involved in the provision of drugs, devices, and health services to treat the disease (Herzlinger 2006).

Attempting to manage this complex system

It can be argued that the goal of managing healthcare systems is to ensure the *quality* of care. The US Institute of Medicine has long defined quality based on six domains: safety, effectiveness, timeliness, efficiency, equity, and patient-centeredness (Institute of Medicine 2001). Since then, others have also considered the experience of care (including patient and provider experience) as a dimension to healthcare quality (Department of Health 2008). Healthcare managers, practitioners and researchers alike are thus concerned with ensuring quality healthcare by focusing on issues such as controlling costs and the underuse, overuse, and misuse of care, avoiding waste, delay, and duplication (Alderwick et al. 2017), and reducing unwarranted variations in care, to name a few. As discussed in Section 1.1, an increasing and aging population, rising burden of chronic disease, ever-increasing healthcare expenditure and growing demand for patient engagement has accentuated the importance of healthcare quality but has also made healthcare management that much more difficult.

There have been countless attempts, both successful and unsuccessful, to deliver quality improvements. These include restructuring, reengineering, and redesign efforts (Grossmann et al. 2011) of healthcare processes that have resulted in new clinical practices, new care models, and new payment mechanisms. As the preceding subchapters demonstrate, sometimes initiatives to improve healthcare quality fail to deliver the desired outcomes, create perverse incentives[3] for

[3] An interesting example relates to the "risk of abundant quality". This refers to "a situation in which changes conceived as *important and beneficial by all stakeholders* are implemented but result in unexpected new hazards, including increased direct and indirect costs, new errors and adverse events, and lost opportunities elsewhere" (Grossmann et al. 2011). As described by (Grossmann et al. 2011), in order to comply with Joint Commission Core Measures, acute care facilities offer pneumococcal vaccinations for hospital inpatients resulting in an increase in redundant vaccinations. While the evidence regarding the safety of multiple vaccinations remains inconclusive (Grossmann et al. 2011), Shih et al. 2002 report on increased adverse events. Moreover, such processes are better suited for and more appropriately measured in primary care settings (Grossmann et al. 2011). For further examples of initiatives that have struggled to live up to their promise, readers are referred to the discussion on HRRP in Section 3.2.5 and the criticisms of various payment methods in healthcare in Table 3.3.

stakeholders, invoke unintended consequences, and stress or introduce negative externalities to the remaining system. Recall that hSCM is a way to decomplexify the healthcare system so that it can be managed, and that a hSC is defined as as *a subsystem of the broader, more complex, healthcare system that (a) is sufficiently simple so that it can be optimized as a subsystem, and (b) this optimization does not create spillovers to the remaining system*. Thus, considered through a hSCM perspective, unsuccessful initiatives fail to satisfy both characteristics of our revised hSCM definition. This naturally leads to the question of how hSCM can be used to design, evaluate, implement, and sustain successful initiatives that improve the quality of healthcare.

The role of modelling research in hSCM

Modelling research in hSCM can help identify improvement opportunities in hSCs and conceptualize and design interventions (e.g., new care models, pathways, payment schemes, etc.). To do so, modelers must first determine the *targeted scope*, or in other words, the boundaries of the hSC. In accordance with our revised definition of hSCM, modelers must identify a subsystem that is sufficiently simple so that in can be "locally optimized". Several points merit further discussion.

Firstly, to determine the targeted hSC, modelers need to consider all of the relevant *stakeholders* that will be impacted by the intervention and their *incentives*. When the success of an intervention hinges on the actions of different stakeholders, ensuring their buy-in is critical. Failing to incorporate all interested parties into the hSC can be the determining factor in whether an intervention will produce the desired outcomes. Herzlinger (2006) offers an example of this in discussing a medical device company whose product innovation ultimately failed, in part, due to this. "The company's product, an instrument for performing noninvasive surgery to correct acid reflux disease, simplified an expensive and complicated operation, enabling gastroenterologists to perform a procedure usually reserved for surgeons. The device would have allowed surgeons to increase the number of acid reflux procedures they performed" (Herzlinger 2006). While the product, and subsequently, the care delivery affected both surgeons and gastroenterologists, the company targeted training towards only the gastroenterologists and failed to secure buy-in from surgeons, ultimately resulting in a "turf war". Herzlinger (2006) counters this example with

Medtronic, who effectively rolled out implantable heart defibrillators. Part of the company's success can be attributed to the fact that "it worked directly with the surgeons who would be implanting them so that the company could identify problems and set procedures" (Herzlinger 2006).

Secondly, another critical aspect to determining the scope of the hSC is to identify all of the relevant *processes* to be targeted by an intervention. Grossmann et al. 2011, describe an effort undertaken by University of Pennsylvania Health System (UPHS) to increase outpatient capacity. Taking a systems view, UPHS conducted major analysis to understand capacity across all care processes including examination rooms, providers, and clerical staff. This involved tracking the key steps in the patient journey from admission to discharge. Through this approach UPHS uncovered a 50% difference between provider capacity and actual capacity (for instance, "patient demand to see a doctor on a Tuesday or Wednesday significantly exceeded capacity, while there was excess room capacity on Friday afternoons" (Grossmann et al. 2011)). This led to the introduction of incentives to encourage use of the room in off-peak times and the harmonization of capacity across clerical staff capacity, exam room availability and physicians[4]. In characterizing the hSC, missing out elements of the processes involved, such as the exam room capacity, may have resulted in key bottlenecks being overlooked and the design of solutions that do not address the core capacity problems.

The main implication demonstrated by the above-discussed examples is that modelers need to carefully consider and understand the hSC before delving into optimization and the design of interventions. To do this, modelers should work closely with practitioners to inform their research and, to some extent, take an "ethnographic research approach" to familiarize themselves with the system. A good example of this approach is provided by the dementia "Golden Ticket" project

[4] Related to the discussion on information sharing in Section 3.2.5, UPHS also introduced an electronic board that tracks the status of inpatients and shares this information in real-time to all care members. "Giving the critical information to staff members allows them to focus on being doctors, nurses, social workers, or transporters rather than wasting time tracking down information that is already available. This initiative created the equivalent of 17 new beds, avoiding $34 million in construction costs and improving the patient, family, and physician experience" (Grossmann et al. 2011).

carried out by the NHS High Weald Lewes Havens Clinical Commissioning Group. The project's aim was to redesign the dementia care pathway, characterized by fragmented access to information, support and care. Before the design of the new care model began, or before the project groups were even formed, the initiative started with a thorough assessment of the current system. "Over the course of six months, a core project team – working closely with partners across the health and social care system, including people with dementia and their carers – *built up a detailed picture* of *how care was being delivered* and *what needed to happen* to improve people's care experience and quality of life. After securing buy-in from senior leaders in local primary care, community care, acute care, social care and voluntary sector organizations, a series of project groups, involving clinicians and people with dementia and their carers, was set up to design and develop the core aspects of a new care model" (Alderwick et al. 2017). This led to the development of a "Golden Ticket" issued to a dementia patient that provides them with a coordinated care package in their community. The new care model resulted in positive outcomes such as a reduction in GP consultations, acute care attendances and admissions as well as an improvement on the quality of life and wellbeing of people with dementia and their carers (Alderwick et al. 2017).

The role of empirical research in hSCM

Although modelling research can optimize a hSC (or equivalently, a subsystem), interventions may carry consequences to the remaining system. The "externalities" or "spillovers" introduced as a consequence can be both positive and negative. Positive spillovers tend to occur due to knowledge spillovers, i.e., where agents "learn" as a result of the intervention or because there are commonalities in production shared between targeted and non-targeted units (e.g., patients, tasks, etc.) (Francetic et al. 2022, Britteon et al. 2023). For instance, consider the UK Quality and Outcome Framework (QOF), a pay-for-performance scheme that incentivizes the recording of certain risk factors for targeted patients (i.e., patients with specific diagnosis codes). As reported by Francetic et al. (2022), "Untargeted patients (those without the specific diagnosis codes targeted) were found to have experienced positive spillover effects as general practitioners also increased their recording of specified risk factors for patients not targeted by the policy". The authors also point to various programs (such as a body mass reduction program and a colorectal

cancer screening program) which "spilled onto" non-targeted individuals through peer and network effects. Negative spillovers occur as a result of the redeployment of existing resources (i.e., the reallocation of resources towards targeted areas by drawing resources away from untargeted areas) or the use of resources which could have been put to better use elsewhere in the system[5] (Francetic et al. 2022).

Britteon et al. (2023) discuss the Best Practice Tariff (BPT) scheme, another UK pay-for-performance scheme that incentives hospitals to treat *certain* elective procedures as day cases. Day cases (in which patients are admitted and discharged on the same calendar day) are typically cheaper than overnight admission, can free up capacity, and have quality advantages (such as higher patient satisfaction and less risk of hospital acquired infection) (Britteon et al. 2023). Using an interrupted time series model and patient-level data from Hospital Episode Statistics, the authors evaluate whether BPT incentives had positive and negative spillovers on non-targeted patients. An example of a negative spillover would include the delayed treatment of non-targeted patients to ensure targeted patients were treated first so that they may recover and be discharged on the same day. Conversely, a positive spillover would refer to improvements in the care of non-targeted patients due to increased investments in shared resources (such as hiring additional staff) or learning effects (such as physicians changing their treatment style in moving away from overnight admissions). Two major findings of the research include that 1) "positive spillover effects of the scheme were almost exclusively concentrated on patients undergoing a non-targeted procedure in an incentivized specialty, where patients were more likely to have shared commonalities in production and to have been treated by a physician that also treated a targeted patient", and 2) "the lack of any initial negative short-term spillover effect supports previous observations that hospitals made real improvements to their daycase capacity instead of reallocating effort and resources away from other patients" (Britteon et al. 2023).

Although modelers and designers of healthcare interventions should consider any possible spillovers, empirical research such as that detailed in the papers described above is critical in

[5] Other mechanisms of (positive and negative) spillovers include effort diversion, gaming, word-of-mouth, improvement in skills and capabilities, among others. Readers are referred to Francetic et al. (2022) for a more comprehensive discussion of mechanisms.

assessing the overall effectiveness of an improvement initiative. Failure to do so can under or overestimate the true impact of an intervention (Francetic et al. 2022). “In particular, studies using non-targeted areas of care as a control group to estimate the targeted effect of a scheme may be downwardly or upwardly biased if the non-targeted area of care was positively or negatively affected by the reform” (Rubin, 1990). “Determining the sign and magnitude of spillover effects has important implications for the optimal design of an incentive scheme” (Britteon et al. 2023). In evaluating interventions, research should thus consider how to maximize positive spillovers and avoid negative spillovers. Importantly, null results, can reassure modelers that the *optimization did not create spillovers to the remaining system*, satisfying the second characteristic of our hSC definition. Equivalently, one may ask: “can the hSC be *pulled out* of the remaining system and be offered as a stand-alone service without having any effect on the broader system?” If the answer is “no”, the subsystem is not correctly determined so that it can be optimized and manageable.

How can improvement initiatives be successfully implemented and sustained in hSCs?

Thus far, the subchapter has considered how hSCM can be used as a way to design and evaluate interventions that improve healthcare quality, but what determines whether such initiatives are sustained in hSCs? The final section of the reflection sheds light on this question.

It is important to recognize that the success and sustainability of an intervention greatly depends on the efforts and actions of stakeholders. Although an initiative may look “great on paper”, its implementation and resulting outcomes can be far from what is expected. Complex systems are made up of many interacting agents with “discretion to repel, ignore, modify, or selectively adopt top-down mandates” (Braithwaite 2018). A core principle in quality improvement is that the stakeholders (e.g., frontline care providers) closest to the root problems are often in the best position to find solutions (Jabbal 2017). Since policy mandated change rarely delivers the same effect as clinically driven change, enabling clinicians to be involved in the decisions that affect their work can be critical for the acceptance of change (Braithwaite 2018). This may prove difficult and requires a change in mindset since according to one survey of healthcare professionals “over 80% of respondents believe doctors have little ability to change the system” (Braithwaite 2018).

Moreover, the importance of slack resources should not be underestimated. As mentioned previously, clinician time is a valuable but scarce resource. Without finding ways to free up staff time so that time and effort can be devoted to a change initiative, clinicians are unlikely to change their practices (Alderwick et al. 2017). Furthermore, "systems reject change when more policies and procedures are issued on top of a multiplicity of exciting policies and procedures" (Braithwaite 2018). This suggests that interventions should be relatively easy to execute, and the value of the intervention should be clearly communicated to all concerned stakeholders. For instance, clinicians may change due to intrinsic motivation to improve the quality of care for their patients and be less concerned with interventions focused on cutting costs (Alderwick et al. 2017).

Another key facet of an initiative's sustainability is measurement to ensure that the intervention continues to deliver the desired outcomes. In the words of Peter Drucker, "*what gets measured, gets done*". Firstly, related to the argument on slack resources, if measurements to track and assess the impact of the intervention are cumbersome to collect and analyze, this may jeopardize data availability. In addition, it is important to consider the types of measures collected. It is critical to capture both process data and outcome data. For instance, although it is valuable to track whether a provider has followed a treatment process, it is also important to capture whether this has resulted in an improvement in patients' health (Herzlinger 2006). Seondly, it is imperative that outcome data is not only captured but clearly associated to the intervention, over the long run. The reason for this is that stakeholders such as insurers "tend to analyze their costs in silos, they often don't see the link between a reduction in hospital labor costs and the new technology responsible for it; they see only the new costs associated with the technology" (Herzlinger 2006). To ensure continued support from stakeholders, an intervention's value should be continuously demonstrated. Lastly, as discussed in the previous subchapters, measurement systems such as performance targets (wait time targets, targeted readmission rates, etc.) can create unanticipated behavior. Thus, it is paramount to consider possible perverse incentives introduced with the rollout of new performance indicators.

In a nutshell…

As stated by Grossmann et al. (2011), "If care delivery systems are to be redefined to meet prospective healthcare demands for improved clinical and financial outcomes, there must be a dramatic change in healthcare culture from siloed to *systems thinking*". Chapter 3 takes this line of thought a step further and argues that the complexity of the healthcare ecosystem requires the adoption of *supply chain thinking*, characterized by a customer focus, systems approach, and a strategic orientation (Mentzer et al. 2001). As a framework, *healthcare* SCM combines SC thinking with a *clinical* dimension (i.e., any action or change within a healthcare system should be motivated and guided by the needs and requirements of patients), *operational* dimension (comprises the technologies and care models that enable operationalization of the transformation) and *financial* dimension (ensures the cost–effectiveness of the improvement and requires creation and placement of appropriate incentives). hSCM should be considered as a tool to decomplexify the healthcare system so that it can be managed. Specifically, a hSC (i.e., a subsystem of the wider healthcare system) can be manageable if *(a) it is sufficiently simple so that it can be optimized as a subsystem (in other words, a standalone SC), and (b) this optimization does not create spillovers to the remaining system.* Modelling research can locally optimize a hSC and devise interventions to improve healthcare quality. This necessitates a careful consideration of the boundaries of the hSC so that it is sufficiently simple to be optimized. Robust empirical research can gauge whether the optimization created spillovers to the remaining system. If not, the boundaries of the hSC have been correctly set. The existence of spillovers suggest that the boundaries of hSC are farther-reaching than those initially determined. Several factors are important in ensuring the successful implementation and sustainability of an intervention in hSCs. These include the engagement and buy-in of the relevant stakeholders, and the careful and continuous measurement of the intervention's performance.

References

Agarwal, A., R. Shankar, M.K. Tiwari. 2006. Modelling the metrics of lean, agile and leagile supply chain: An ANP–based approach. *European. Journal Operations Research* 173:211–225.

Alderwick, H. A. Charles, B. Jones, et al. 2017. *Making the case for quality improvement: lessons for NHS boards and leaders.* (The King's Fund, London).

Alderwick, H., C. Ham, D. Buck. 2015. *Population health systems: Going beyond integrated car*e (The King's Fund, London).

Amgen. 2017. Amgen and Harvard Pilgrim agree to first cardiovascular outcomes–based refund contract for Repatha®(Evolocumab). Available at: https://www.amgen.com/media/news–releases/2017/05/amgen–and–harvard–pilgrim–agree–to–first–cardiovascular–outcomesbased–refund–contract–for–repatha–evolocumab/. Accessed August 13, 2020.

Andritsos, D.A., C.S. Tang. 2018. Incentives programs for reducing readmissions when patients care is co–produced. *Production Operations Management* 27(6):999–1020.

Aronsson, H., M. Abrahamsson, K. Spens. 2011. Developing lean and agile healthcare supply chains. *Supply Chain Management* 16(3):176–183.

Avansino, J.R., A.B. Goldin, R. Risley, J.H.T. Waldhausen, R.S. Sawin. 2013. Standardization of operative equipment reduces cost. *Journal of Pediatric Surgery* 48(9):1843–1849.

Ayer, T., Q. Chen. 2018. Personalized medicine. Dai T., Tayur S., eds. *Handbook of healthcare analytics: theoretical minimum for conducting 21st century research on healthcare operations* (Wiley, New York), 109–136.

Babich, V., G. Hilary. 2019. Distributed ledgers and operations: What operations management researchers should know about blockchain technology. *Manufacturing & Service Operations Management* 22(2):223–240.

Bach, P.B. 2010. A map to bad policy: Hospital efficiency measures in the Dartmouth Atlas. *New England Journal of Medicine* 362(7):569–574.

Bare, A. 2015. Pooled procurement in the vaccine market: UNICEF's experience. Report, William Davidson Institute, University of Michigan, Ann Arbor.

Barua, B., D. Jacques, A. Collyer. 2018. *Waiting your turn: Wait times for healthcare in Canada*, 2018 Report (Fraser Institute, British Columbia, Canada).

Bauer, U.E., P.A. Briss, R.A. Goodman, B.A. Bowman. 2014. Prevention of chronic disease in the 21st century: Elimination of the leading preventable causes of premature death and disability in the USA. *Lancet* 384:45–52.

Bavafa, H., L.M. Hitt, C. Terwiesch. 2018. The impact of e–visits on visit frequencies and patient health: Evidence from primary care. *Management Science* 64(12):5461–5480.

Berwick, D.M., T.W. Nolan, J. Whittington. 2008. The triple aim: Care, health, and cost. *Health Affairs* 27(3):759–769.

Betcheva, L., F. Erhun, H. Jiang. 2019. Healthcare supply chains. Choi T., Li J.J., Rogers D., Rungtusanatham M.J., Schoenherr T., Wagner S., eds. *The Oxford Handbook of Supply Chain Management* (Oxford University Press, New York).

Betz, M. 2018. The new nonprofit pharmaceutical world: What's up with that? Available at: https://nonprofitquarterly.org/the–new–nonprofit–pharmaceutical–world–whats–up–with–that/. Accessed May 29, 2020.

Bloomberg. 2020. Coronavirus: Supply chain disruption looks like natural disasters. Available at: https://www.supplychainbrain.com/articles/30953–coronavirus–supply–chain–disruption–looks–like–natural–disasters. Accessed February 27, 2020.

Boddy, N. 2019. Improving communication to general practitioners at hospital discharge: A systems approach. Dissertation, University of Cambridge, Cambridge, UK.

Bottery, S., M. Varrow, R. Thorlby, D. Wellings. 2018. A fork in the road: Next steps for social care funding reform. Available at: https://www.kingsfund.org.uk/sites/default/files/2018–05/A–fork–in–the–road–next–steps–for–social–care–funding–reform–May2018.pdf. Accessed May 2, 2019.

Braithwaite, J. 2018. Changing how we think about healthcare improvement. *The British Medical Journal* 361:k2014.

Bretthauer, K.M., S.H. Heese, H. Pun, E. Coe. 2011. Blocking in healthcare operations: A new heuristic and an application. *Production Operations Management* 20(3):375–391.

Brindle, D. 2017. Buurtzorg: The Dutch model of neighborhood care that is going global. *The Guardian* (May 9). Available at: https:// www.theguardian.com/social–care–network/2017/may/09/buurtzorg–dutch–model–neighbourhood–care.

Britteon, P., S. Kristensen, Y. Lau, R. McDonald, M. Sutton. 2023. Spillover effects of financial incentives for providers onto non-targeted patients: Daycase surgery in English hospitals. *Health Economics, Policy and Law* 18(3): 289–304.

Buck, D., A. Baylis, D. Dougall, R. Robertson. 2018. A vision for population health: Towards a healthier future. The King's Fund. Available at: https://www.kingsfund.org.uk/publications/vision–population–health. Accessed January 18, 2023.

Cachon, G., C. Terwiesch. 2009. *Matching supply with demand: An introduction to operations management* (McGraw–Hill, Singapore). Campbell H, Hotchkiss R, Bradshaw N, Porteous M (1998) Integrated care pathways. *BMJ* 316:133–144.

Champagne, D., S. Chilukuri, M. Imprialou, S. Rathore, J. VanLare. 2018. Machine learning and therapeutics 2.0: Avoiding hype, realizing potential. Report, McKinsey & Company, New York.

Charles, A. 2019. Community health services explained. Available at: https://www.kingsfund.org.uk/publications/community–health–services–explained\#how–are–they–organised. Accessed May 2, 2019

Chen, C.J., N. Savva. 2018. Unintended consequences of hospital regulation: The case of the Hospital Readmissions Reduction Program. Working paper, London Business School, London.

Christensen, C.M., J.H. Grossman, J. Huang. 2017. *The innovator's prescription: A disruptive solution for healthcare* (McGraw Hill Education, New York).

Christopher, M.L. 2016. *Logistics and supply chain management*, 5th ed. (Pearson Education, Harlow, UK).

Civica Rx. 2019. Hikma and Civica Rx sign long–term agreement. Available at: https://civicarx.org/media/#press. Accessed August 13, 2020.

CMS. 2017. Hospital value–based purchasing. Available at: https://www.cms.gov/Outreach–and–Education/Medicare–Learning–Network–MLN/MLNProducts/downloads/Hospital_ VBPurchasing _Fact_Sheet_ICN907664.pdf. Accessed August 13, 2020.

Collins, B. 2016. *New care models: Emerging innovations in governance and organization form* (The King's Fund, London).

Cox, B., F. Erhun, S. Scholtes. 2016. Review of the Uniting Care Partnership contract termination. Technical report, Judge Business School, University of Cambridge, UK.

Coxa. 2017. Coxa lowers prices and expands: Society saves two million a year. News release. Available at: https://www.coxa.fi/en/coxa–lowers–prices–and–expands–society–saves–two–million–a–year/. Accessed August 13, 2020,

Cyranoski, D. 2020. What China's coronavirus response can teach the rest of the world. *Nature* 579(7800):479–480.

Dai, T., S. Tayur. 2020. Healthcare operations management: A snapshot of emerging research. *Manufacturing & Service Operations Management* 22(5):869–887.

Dartmouth Atlas. 2019. The Dartmouth Atlas of Health Care. Available at: https://www.dartmouthatlas.org/. Accessed August 13, 2020,

de Vries, J., R. Huijsman. 2011. Supply chain management in health services: An overview. *Supply Chain Management* 16(3):159–165.

del Castillo, M. 2016. Hyperledger project explores counterfeit drugs with blockchain. Available at: https://www.coindesk.com/hyperledger–counterfeit–drugs–blockchain. Accessed August 13, 2020.

Department of Health. 2008. High quality care for all: NHS next stage review final report. Available at: https://www.gov.uk/government/publications/high-quality-care-for-all-nhs-next-stage-review-final-report. Accessed July 19, 2023.

Digest SC. 2006. The 11 greatest supply chain disasters. Available at: http://www.scdigest.com/assets/reps/SCDigest_Top–11–SupplyChainDisasters.pdf. Accessed August 13, 2020,

Dowdeswell, B., E. Vauramo. 2009. Coxa Hospital, Tampere, Finland. Rechel B., Erskine J., Dowdeswell B., Wright S., McKee M., eds. *Capital investment for health: Case studies from Europe*, Observatory Studies Series, no. 18 (The European Observatory on Health Systems and Policies, WHO Regional Office for Europe, Copenhagen), 27–39.

Engelhardt, M.A. 2017. Hitching healthcare to the chain: An introduction to blockchain technology in the healthcare sector. *Technology Innovation Management Review* 7(10):22–34.

Erhun, F., P. Keskinocak. 2011. Collaborative supply chain management. Kempf K.G., Keskinocak P., Uzsoy R., eds. *Planning Production and Inventories in the Extended Enterprise* (Springer, Boston), 233–268.

Erhun, F., R.S. Kaplan, V.G. Narayanan, K. Brayton, M. Kalani, M.C. Mazza, C. Nguyen et al. (2019) Are modern Indian hospital cost advantages transferable to US peers? Working paper, Judge Business School, University of Cambridge, UK.

Evgeniou, T., D.R. Hardoon, A. Ovchinnikov. 2020. Leveraging AI to battle this pandemic: And the next one. Available at: https://hbr.org/2020/04/leveraging–ai–to–battle–this–pandemic–and–the–next–one. Accessed August 13, 2020.

EHMA (European Health Management Association). Understanding health management. Available at: https://ehma.org/about-health-management/#:~:text=Healthcare%20management%20is%20the%20practice,effectiveness%2C%20efficiency%2C%20and%20equity. Accessed July 19, 2023.

Fedyanova, Y. 2018. Incentivizing young doctors to practice in underserved areas. *Canadian Medical Association Journal* 190(7):e203.

Finch, D., J. Bibby, T. Elwell–Sutton. 2018. Briefing: Taking our health for granted: Plugging the public health grant funding gap. Available at: https://www.health.org.uk/sites/default/files/upload/publications/2018/Taking%20our%20health%20for%20granted_for%20web.df. Accessed August 13, 2020.

Finlay, S. 2018. *Artificial intelligence and machine learning for business: A no–nonsense guide to data driven technologies.* (Relativistic, Preston, UK).

Fisher, E.S., D.O. Staiger, J.P. Bynum, D.J. Gottlieb. 2007. Creating accountable care organizations: The extended hospital medical staff. *Health Affairs (Millwood)* 26(1):w44–w57.

Fisher, M.L. 1997. What is the right supply chain for your product? *Harvard Business Review* 75(2):105–116.

Foster, K., P. Penninti, J. Shang, S. Kekre, G.G. Hegde, A. Venkat. 2018. Leveraging big data to balance new key performance indicators in emergency physician management networks. *Production Operations Management* 27(10):1795–1815.

Francetic, I., R. Meacock, J. Elliot, S.R. Kristensen, P. Britteon, D.G. Lugo-Palacios et al. 2022. Framework for identification and measurement of spillover effects in policy implementation: intended and non-intended targeted non-targeted spillovers (INTENTS). *Implementation Science Communications* 3(1):30.

Freeman, M., N. Savva, S. Scholtes. 2020. Economies of scale and scope in hospitals: An empirical study of volume spillovers. *Management Science* 67(2):673–697.

Gandhi, A., C. Magar, R. Roberts. 2013. How technology can drive the next wave of mass customization. *McKinsey on Business Technology* 32(Winter):1–8.

Gmeinder, M., D. Morgan, M. Mueller. 2017. How much do OECD countries spend on prevention? OECD Health Working Papers No. 101, Organisation for Economic Co–operation and Development, Paris.

Goran, S.F. 2010. A second set of eyes: An introduction to Tele–ICU. *Critical Care Nurse* 30(4):46–55.

Govindarajan, V., R. Ramamurti. 2013. Delivering world–class healthcare, affordably. *Harvard Business Review* 91(11):117–122.

Gov.uk. 2010. Coxa hospital for joint replacement. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/466902/Appendix_B_Coxa_International_Case_Study.pdf. Accessed August 13, 2020.

Grean, M., M.J. Shaw. 2002. Supply chain partnership between P&G and Wal–Mart. Shaw M.J., ed. *E–business management: integration series in information systems* (Springer, Boston), 155–171.

Green, L.V. 2012. OM forum: The vital role of operations analysis in improving healthcare delivery. *Manufacturing & Service Operations Management* 14(4):488–494.

Gröne, O., M. Garcia–Barbero. 2001. Integrated care: A position paper of the WHO European Office for integrated healthcare services. *International Journal of Integral Care* 1(1):1–10.

Grossmann, C., W. Goolsby, L. Olsen, J. McGinnis. 2011. *Engineering a Learning Healthcare System: A Look at the Future.* Workshop Summary. Washington, DC: National Academies Press.

Guha, S., S. Kumar. 2018. Emergence of big data research in operations management, information systems, and healthcare: Past contributions and future roadmap. *Production Operations Management* 27(9):1724–1735.

Guo, P., C.S. Tang, Y. Wang, M. Zhao. 2019. The impact of reimbursement policy on social welfare, revisit rate, and waiting time in a public healthcare system: Fee–for–service vs. bundled payment. *Manufacturing & Service Operations Management* 21(1):154–170.

Hajat, C., E. Stein. 2018. The global burden of multiple chronic conditions: A narrative review. *Preventive Medicine Reports* 12:284–293.

Hamburg, M.A., F.S. Collin. 2010. The path to personalized medicine. *New England Journal of Medicine* 363:301–304.

Herzlinger, R.E. 2006. Why innovation in health care is so hard. *Harvard Business Review* 84: 58–66.

Hildebrandt, H., C. Hermann, R. Knittel, M. Richter–Reichhelm, A. Siegel, W. Witzenrath. 2010. Gesundes Kinzigtal integrated care: Improving population health by a shared health gain approach and a shared savings contract. *International Journal of Integrated Care* 10:e046.

Hoff, T., W. Weller, M. DePuccio. 2012. The patient–centered medical home: A review of recent research. *Medical Care Research and Review* 69(6): 619–644.

Imperial College London. 2020. Covid–19 reports. Available at: https://www.imperial.ac.uk/mrc–global–infectious–disease–analysis/covid–19/covid–19–reports/. Accessed August 13, 2020.

Institute of Medicine. 2001. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Washington, D.C.: National Academy Press.

Jabbal, J. 2017. *Embedding a culture of quality improvement.* (The King's Fund, London).

James, J. 2013. Medicare hospital readmissions reduction program. Health affairs health policy brief. Available at: https://www.healthaffairs.org/do/10.1377/hpb20131112.646839/full/ healthpolicybrief_102.pdf. Accessed August 13, 2020.

Jameson, J.L., D.L. Longo. 2015a. Precision medicine: Personalized, problematic, and promising. *New England Journal of Medicine* 372:2229–2234.

Jameson, J.L., D.L. Longo. 2015b. Precision medicine: Personalized, problematic, and promising (editorial comment). *Obstetrics Gynecological Survey* 70:612–614.

Jiang H, Sodhi MS (2019) Analyzing the proposed reconfiguration of accident–and–emergency facilities in England. *Production Operations Management* 28(7):1837–1857.

Joynt KE, Figueroa J, Oray J, Jha AK (2016) Opinions on the hospital readmission reduction program: Results of a national survey of hospital leaders. American Journal of Managed Care 22(8):e287–e294.

Kaplan EH (2020) COVID–19 scratch models to support local decisions. *Manufacturing & Service Operations Management* 22(4):645–655.

Kavadias S, Ladas K, Loch C (2016) The transformative business model. *Harvard Business Review* 94(10):90–98.

KC DS, Scholtes S, Terwiesch C (2020) Empirical research in healthcare operations: Past research, present understanding, and future opportunities. *Manufacturing & Service Operations Management* 22(1):73–83.

KC DS, Terwiesch C (2011) The effects of focus on performance: Evidence from California hospitals. *Management Science* 57(11):1897–1912.

Kenney C (2011) *Transforming Healthcare: The Virginia Mason Medical Center Story* (Productivity Press, New York).

Keskinocak P, Savva N (2020) A review of the healthcare management (modeling) literature published in *Manufacturing& Service Operations Management. Manufacturing & Service Operations Management* 22(1):59–72.

Kraljic P (1983) Purchasing must become supply management. *Harvard Business Review* 61(5):109–117.

Kuntz L, Scholtes S, Sülz S (2019) Separate and concentrate: Accounting for patient complexity in general hospitals. *Management Science* 65(6):2482–2501.

Lee, T.H. 2015. Financial vs. non–financial incentives for improving patient experience. *Journal of Patient Experience* 2(1):4–6.

Liu X, Hu M, Helm JE, Lavieri MS, Skolarus TA (2018) Missed opportunities in preventing hospital readmissions: Redesigning post–discharge checkup policies. *Production Operations Management* 27(12):2226–2250.

Livingston EA, Desai M, Berkwits M (2020) Sourcing personal protective equipment during the COVID–19 pandemic. *JAMA* 323(19):1912–1914.

Lovell N, Bibby J (2018) What makes us healthy? An introduction to the social determinants of health. Available at: https://www.health.org.uk/sites/default/files/What–makes–us–healthy–quick–guide.pdf. Accessed August 13, 2020.

Marr, B. 2017. This is why blockchains will transform healthcare. Available at: https://www.forbes.com/sites/bernardmarr/2017/11/29/this–is–why–blockchains–will–transform–healthcare/#e015d591ebe3. Accessed August 13, 2020.

Marshall, L., D. Finch, L. Cairncross, J. Bibby. 2018. Briefing: The nation's health as an asset. Available at: https://www.health.org.uk/sites/default/files/upload/publications/2018/The%20nation%27s%20health%20as%20an%20asset.pdf. Accessed August 13, 2020.

Mattiuzzi, C., G. Lippi. 2020. Which lessons shall we learn from the 2019 novel coronavirus outbreak? *Annals of Translational Medicine* 8(3):48.

Mentzer, J., W. DeWitt, J. Keebler, S. Min, N.W. Nix, C.D. Smith, Z. Zacharia. 2001. Defining supply chain management. *Journal of Supply Chain Management* 22(2):1–25.

Mettler, M. 2016. Blockchain technology in healthcare: The revolution starts here. *IEEE 18th International Conf. e–Health Networking Application & Services* (IEEE, Munich, Germany), 1–3.

Minvielle, E. 2018. Toward customized care: Comment on "(Re)making the procrustean bed? Standardization and customization as competing logics in healthcare." *International Journal Health Policy Management* 7(3):272–274.

Minvielle, E., M. Waelli, C. Sicotte, J.R. Kimberly. 2014. Managing customization in healthcare: A framework derived from the services sector literature. *Health Policy* 117:216–227.

Miotto, R., F. Wang, S. Wang, X. Jiang, J.T. Dudley. 2018. Deep learning for healthcare: Review, opportunities and challenges. *Brief. Bioinformatics* 19(6):1236–1246.

Moore, W.C., D.A. Meyers, S.E. Wenzel, W.G. Teague, H. Li, X. Li, R. D'Agostino Jr et al. 2010. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *American Journal of Respiratory Critical Care Medicine* 181:315–323.

Mount Sinai Hospital. 2016. Spreading Sinai Health System's successful ACE Strategy across Canada. Available at: https://www.mountsinai.on.ca/about_us/news/2016–news/spreading–sinai–health–systems–successful–ace–strategy–across–Canada. Accessed August 13, 2020.

Neville, S. 2019. NHS looks to artificial intelligence to improve healthcare. *Financial Times* (August 8), Available at: https://www.ft.com/content/c0b3be56–b922–11e9–96bd–8e884d3ea203.

NHS England. 2016. The multispecialty community provider (MCP) emerging care model and contract framework. Available at: https://www.england.nhs.uk/wp–content/uploads/2016/07/mcp–care–model–frmwrk.pdf. Accessed August 13, 2020.

NHS England. 2018. Report of the review of the quality and outcomes framework in England. Available at: https://www.england.nhs.uk/wp–content/uploads/2018/07/05–a–i–pb–04–07–2018–qof–report.pdf. Accessed August 13, 2020,

NHS England and NHS Improvement. 2020. Important and urgent: Next steps on NHS response to Covid–19. Available at: https://www.england.nhs.uk/coronavirus/wp–content/uploads/ sites/52/2020/03/ urgent–next–steps–on–nhs–response–to–covid–19–letter–simon–stevens.pdf. Accessed August 13, 2020.

Norris, P. 2007. Skeptical Patients: Performance, Social Capital, and Capital. In D.A. Shore (ed.), *The trust crisis in healthcare: Causes, consequences, and cures* (pp. 32–46). New York: Oxford University Press.

Ody, C., L. Msall, L.S. Dafny, D.C. Grabowski, D.M. Cutler. 2019. Decreases in readmissions credited to Medicare's program to reduce hospital readmissions have been overstated. *Health Affairs* 38(1):36–43.

Oliver, A. 2008. Public–sector health–care reforms that work? A case study of the US Veterans Health Administration. *Lancet* 371(5):1211–1213.

Perreault, L., Q. Pan, K. Mather, K.E. Watson, R.F. Hamman, S.E. Kahn. 2010. Effect of regression from prediabetes to normal glucose regulation on long–term reduction in diabetes risk: Results from the diabetes prevention program outcomes study. *Lancet* 379(9833):2243–2251.

PhRMA. 2016. 2016 biopharmaceutical research industry profile. Available at: http://phrma–docs.phrma.org/sites/default/files/pdf/biopharmaceutical–industry–profile.pdf. Accessed August 13, 2020.

Pinker, E.J. 2012. Commentaries to "The vital role of operations analysis in improving healthcare delivery." *Manufacturing & Service Operations Management* 14(4):495–511.

Porter, M.E. and E.O. Teisberg. 2006. Redefining Health Care: Creating Value-Based Competition on Results. Boston, M.A.: Harvard Business School Press.

Queenan, C., K. Cameron, A. Snell, J. Smalley, N. Joglekar. 2019. Patient heal thyself: Reducing hospital readmissions with technology enabled continuity of care and patient activation. *Production Operations Management* 28(11):2841–2853.

Raghupathi, W., V. Raghupathi. 2018. An empirical study of chronic diseases in the United States: A visual analytics approach. *International Journal of Environmental Research and Public Health* 15(3):431.

Ramdas, K., A. Darzi. 2017. Adopting innovations in care delivery: The case of shared medical appointments. *New England Journal of Medicine* 376(12):1105–1107.

Ramdas, K., K. Saleh, S. Stern, H. Liu. 2018. Variety and experience: Learning and forgetting in the use of surgical devices. *Management Science 64*(6):2590–2608.

Roche. 2018. From big data to personalised healthcare: A vision for the NHS in 2030. Available at: http://roche–images.co.uk/design/corporate/rxukcomm01952<inline. Accessed August 13, 2020.

Roden, D.M., J.M. Pulley, M.A. Basford, G.R. Bernard, E.W. Clayton, J.R. Balser, D.R. Masys. 2008. Development of a large–scale deidentified DNA biobank to enable personalized medicine. *Clinical Pharmacology Therapy* 84(3):362–369.

Royal College of Nursing. 2020. Public health. Available at: https://www.rcn.org.uk/clinical–topics/public–health. Accessed August 13, 2020.

Rubin, D.B. 1990. Formal modes of statistical inference for casual effects. *Journal of Statistical Planning and Inference* 25: 279–292.

Savva, N., T. Tezcan, Ö. Yıldız. 2019. Can yardstick competition reduce waiting times? *Management Science* 65(7):3196–3215.

Schorpp, G., F. Erhun, H.L. Lee. 2020. Multi–tiered supply chain risk management. Working paper, Judge Business School, University of Cambridge, Cambridge, UK.

Shactman, D. 2005. Specialty hospitals, ambulatory surgery centers, and general hospitals: Charting a wise public policy course. *Health Affairs* 24(3):868–873.

Sharfstein, J.M., E.A. Stuart, J. Antos. 2018. Global budgets in Maryland: Assessing results to date. *JAMA* 319(24):2475–2476.

Shaw, S., R. Rosen, B. Rumbold. 2011. What is integrated care? Available at: https://www.nuffieldtrust.org.uk/research/what–is–integrated–care. Accessed August 13, 2020.

Shih, A., J. Quinley, T.K. Lee, C.R. Messina. 2002. Assessing pneumococcal revaccination safety among New York state Medicare beneficiaries. *Public Health Reports* 117(2): 164–173.

Song, H., A.L. Tucker, K.L. Murrell. 2015. The diseconomies of queue pooling: An empirical investigation of emergency department length of stay. *Management Science* 61(12):3032–3053.

Tang, C.S., J.D. Zimmerman, J.I. Nelson. 2009. Managing new product development and supply chain risks: The Boeing 787 case. *Supply Chain Forum International Journal* 10(2):74–86.

Taylor, A., E. Escobar, K. Udayakumar. 2017. Expanding access to low–cost, high–quality tertiary care: Spreading the Narayana Health model beyond India. Available at: https://www.commonwealthfund.org/publications/case–study/2017/nov/expanding–access–low–cost–high–quality–tertiary–care\#6. Accessed August 13, 2020.

The Economist Intelligence Unit. 2016. Specialisation and standardisation: Value–based healthcare at Canada's Shouldice Hospital. Available at: https://www.medtronic.com/content/dam/medtronic–com/transforming–healthcare/documents/shouldice–hospital–canada_case_eiu_av_corpmark.pdf. Accessed August 13, 2020.

The King's Fund. 2013. The NHS at 65. Available at: https://www.kingsfund.org.uk/projects/nhs–65. Accessed August 13, 2020.

The Office of the National Coordinator for Health Information Technology. 2019. What are the advantages of electronic health records? Available at: https://www.healthit.gov/faq/what–are–advantages–electronic–health–records. Accessed August 13, 2020.

Thompson, S., J. Whitaker, R. Kohli, C. Jones. 2018. How information technology and analytics create healthcare value: A theory of temporal displacement of care. *Management Information Systems Quarterly* 44(1):227–256.

Thorlby, R. 2013. Reclaiming a population health perspective: Future challenges for primary care. Available at: https://www.nuffieldtrust.org.uk/files/2017–01/reclaiming–a–population–health

perspective–web–final.pdf. Accessed August 13, 2020,

United Nations. 2019. Aging. Available at: https://www.un.org/en/sections/issues–depth/ageing/. Accessed August 13, 2020.

van der Eijk, M., M.J. Faber, J.W.M. Aarts, J.A.M. Kremer, M. Munneke, B.R. Bloem. 2013. Using online health communities to deliver patient–centered care to people with chronic conditions. *Journal of Medical Internet Research* 15(6):e115.

Vickers, T., E. Rosen. 2011. Driving down the cost of high–quality care: Lessons from the Aravind Eye Care System. *Health International* 11:18–27.

Virginia Mason. 2019. Virginia Mason production system. Available at: https://www.virginiamason.org/vmps. Accessed August 13, 2020,

Virginia Mason Medical Center. 2010. VMPS facts. Available at: https://createvalue.org/wp–content/uploads/2013/11/case–study–virginia–mason.pdf. Accessed August 13, 2020.

Volpp, K.G., H.M. Krumholz, D.A. Asch. 2018. Mass customization for population health. *JAMA Cardiology* 3(5):363–364.

Wadhera, R.K., K.E. Joynt Maddox, J.H. Wasfy, S. Haneuse, C. Shen, R.W. Yeh. 2018. Association of the hospital readmissions reduction program with mortality among Medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *JAMA* 320(24):2542–2552.

Wicks, P., D.L. Keininger, M.P. Massagli, C. de la Loge, C. Brownstein, J. Isojärvi, J. Heywood. 2011. Perceived benefits of sharing health data between people with epilepsy on an online platform. *Epilepsy Behavior* 23:16–23.

World Health Organization. 2009. *Telemedicine opportunities and developments in member states: report on the second global survey on ehealth*, Global Observatory for eHealth Series, vol. 2 (World Health Organization, Geneva).

World Health Organization. 2019. Risk pooling for universal health coverage (UHC). Available at: https://www.who.int/health_financing/topics/pooling/risk–pooling/en/. Accessed August 13, 2020.

Yu, K.H., C. Zhang, G.L. Berry, R.B. Altman, C Re, D.L. Rubin, M. Snyder. 2016. Predicting non–small cell lung cancer prognosis by fully automated microscopic pathology image features. *Nature Communications* 7:12474.

Zhang, D.J., I. Gurvich, J. Van Mieghem, E. Park, R. Young, M. Williams. 2016. Hospital readmissions reduction program: An economic and operational analysis. *Management Science* 62(11):3351–3371.

Zuckerman, R.B., S. Sheingold, J. Orav, J. Ruhter, A. Epstein. 2016. Readmissions, observation, and the hospital readmissions reduction program. *New England Journal of Medicine* 374(16):1543–1551.

Supplementary Material

This addendum contains two sections. The first, “Categorization of healthcare supply chains", captures and categorizes the wide array of hSC stakeholders and provides a synopsis of research for these subcategories from four prominent operations management journals. The second, “Challenges in healthcare delivery", discusses the main clinical and public health, operational and financial challenges in healthcare systems.

3.A A Categorization of Healthcare Supply Chains

We divide healthcare supply chains (hSCs) into four categories: health services supply chains (SCs), pharmaceutical SCs, special health services SCs, and health humanitarian SCs (Table 3.A.1). Healthcare service SCs are further divided into subcategories focusing on the flow of patients, providers, finances, and supplies and equipment. Care is provided by physicians in medical SCs and by non–physicians in community and social care SCs. Similarly, pharmaceutical SCs are split into upstream SCs involved in drug discovery and development, and downstream SCs responsible for the manufacture and distribution of approved pharmaceuticals. Finally, special health services SCs are split into blood, organ transplantation, and vaccine SCs.

Note that we do not have a separate category for support services, but it is a critical element of all hSCs. A major component of support services, from a SCM perspective, is health technology. We refer the reader to several papers examining the role and impact of IT and information exchange on healthcare; Angst et al. (2011), Atasoy et al. (2018), Ayer et al. (2019b), Hydari et al. (2019), Lahiri and Seidmann (2012), Oh et al. (2018), Sharma et al. (2019).

We refer the reader to Betcheva et al. (2019) for details on main challenges, risks, and research for these subcategories; Kim and Kwon (2015) for a review of the hSC literature in the US based on research published in 2004–2015 with a focus on comparative studies between commercial and healthcare supply chains, and the major tools and barriers in adopting hSCM; de Vries and

Huijsman (2011) for a review of studies examining hSC integration with regard to information flows, planning processes, intra– and inter–organizational processes, market approach, and market development; Cho and Zhao (2018) for an analysis of hSCs with a focus on pharmaceutical SCs, and Pierskalla (2005) for a review of blood SCs. We build on previous literature by capturing and categorizing the wide array of hSC stakeholders. Additionally, we offer a framework to divide the overarching hSC into subcategories based on the flow of people, products, services, ancillaries, finances, and information.

In this addendum, we provide a synopsis of research for these subcategories. We include ~170 publications in the past decade (2009 onward) from four prominent operations management journals, namely, Manufacturing & Service Operations Management, Management Science, Operations Research, and Production and Operations Management. We acknowledge that our list is not exhaustive, as there exists a large body of healthcare operations management literature that lies outside the aforementioned journals and predates our sample range. Although some of the publications may fit into multiple categories/subcategories, for ease of presentation, we classify each paper under one category/subcategory. Our aim is to provide the reader with an idea of the recent trends in the operations management literature based on our hSC categorization.

Table 3.A.1 hSC categories and subcategories.

hSC	Description
1. Health services SCs	
1.1 Medical SCs	the patient flow across primary, secondary, and tertiary care
1.2 Community and social care SCs	the funding and provision of community, residential, domiciliary, and informal care
1.3 Workforce SCs	the flow of providers in the healthcare sector
1.4 Reimbursement SCs	the flow of finances between payers, providers, and patients for healthcare services
1.5. Supplies and equipment SCs	the procurement, logistics, and inventory management of supplies and the purchase, operation, maintenance, and repair of medical equipment
2. Pharmaceutical SCs	
2.1 Innovation and R&D SCs	the flow of potential medicines through discovery, pre-clinical, and clinical testing to regulatory approval
2.2 Manufacturing and distribution SCs	the flow of approved medicines from manufacturing and distributors to healthcare providers, and ultimately patient end-users
3. Special health services SCs	
3.1 Blood SCs	the collection, testing, processing, storage, distribution, and transfusion of blood and blood products
3.2 Organ transplantation SCs	the flow of organs from living or deceased donors to patients requiring transplantation
3.3 Vaccine SCs	the manufacture, distribution, and provision of vaccines
4. Health humanitarian SCs	the flow of healthcare products and services to humanitarian aid recipients

Table 3.A.2 Health Services SCs: Medical SCs

Key Research Areas	Subareas	Literature
Appointment and patient scheduling	Coordination of multiple appointments/providers	Dong et al. (2019), Wang et al. (2018, 2019a)
	No-show behavior/ cancellations	Cayirli et al. (2012), Diamant et al. (2018), Izady (2015), Li et al. (2019), Liu et al. (2010), Liu (2016), Liu et al. (2019a), Luo et al. (2012), Osadchiy and KC (2017), Robinson and Chen (2010), Samorani and Ganguly (2016)
	Patient preferences and characteristics	Feldman et al. (2014), Lee et al. (2018), Liu et al. (2019b), Salzarulo et al. (2011, 2016), Wang and Gupta (2011), Wang et al. (2019b)
	Data-driven	He et al. (2019), Mandelbaum et al. (2019)
	Elective admission	Helm and Van Oyen (2014), Huh et al. (2013), Meng et al. (2015)
	Overbooking	LaGanga and Lawrence (2012), Lee and Zenios (2009), Liu and Ziya (2014), Zacharias and Pinedo (2014)
	Backlogs	Zacharias and Armony (2017)
	Urgent patients	Deglise-Hawkinson et al. (2018), Dobson et al. (2011)
	Walk-ins and call-ins	Chen and Robinson (2014), Wang et al. (2019c)
	Integration with capacity decisions	Liu et al. (2019c), White et al. (2011)
	Surgery	Chow et al. (2011), Denton et al. (2010), Freeman et al. (2019), Gul et al. (2011), Jung et al. (2019), Ozen et al. (2016)
Patient routing	Transfers	Armony et al. (2018), Hu et al. (2018), Lu and Lu (2017a), Thompson et al. (2009)
	Delayed transfer of care and bed blocking	Bretthauer et al. (2011), Mandelbaum et al. (2012), Samiedaluie et al. (2017), Zychlinski et al. (2019)
	Discharge	Batt and Terwiesch (2015), Chan et al. (2012, 2017a), Dobson et al. (2010), KC and Terwiesch (2012)
	Referrals	Zhang et al. (2012a)
	Diversion	Allon et al. (2013), Deo and Gurvich (2011), Xu and Chan (2016)
	Patient needs	Chan et al. (2019a), Kuntz et al. (2019), Pinker and Tezcan (2013)
	Overflow/outliers	Dai and Shi (2019), Izady and Mohamed (2019), Song et al. (2019)
	Triaging and prioritization	Ding et al. (2019), Huang et al. (2015), Kamali et al. (2019), Mills et al. (2013), Saghafian et al. (2014, 2019)
	Streaming	Saghafian et al. (2012)
	Admission/boarding	Barz and Rajaram (2015), Chan et al. (2017b), Helm et al. (2011), KC and Terwiesch (2017), Kim et al. (2015), Long and Mathews (2018), Price et al. (2011), Shi et al. (2016)
	Arrival	Anderson et al. (2014)
	Readmissions	Helm et al. (2016), Liu et al. (2018), Queenan et al. (2019)
	Continuity of care	Senot (2019)

Table 3.A.3 Health Services SCs: Community and social care SCs

Key Research Areas	Literature
Screening/diagnosis	Ayvaci et al. (2012), Deo et al. (2015), Erenay et al. (2014), Lee et al. (2019), Örmeci et al. (2016)
Public health	Aprahamian et al. (2019), Ayer et al. (2016, 2019a), Chehrazi et al. (2019), Chhatwal et al. (2010), Chen et al. (2018), Goh et al. (2016), Güneş et al. (2014), Mochon et al. (2017), Rauner et al. (2010), Yan (2017), Yang et al. (2013), Zepeda and Sinha (2015)
Scheduling	Deo et al. (2013), Patrick (2011)
Staffing	Lu and Lu (2017b), Lu et al. (2018), Slaugh et al. (2018)
Capacity	Bavafa et al. (2019), Zhang et al. (2012b)
Patient flow	Kucukyazici et al. (2011)
Policy	Han et al. (2018)

Table 3.A.4 Health Services SCs: Workforce SCs

Key Research Areas	Subareas	Literature
Configuration	Workforce staffing and scheduling	He et al. (2012), Kim and Mehrotra (2015), Lemay et al. (2015), Roth et al. (2019), de Véricourt and Jennings (2011), Yankovic and Green (2011), Yom-Tov and Mandelbaum (2014)
	Dispatching	Chong et al. (2016), McLay and Mayorga (2013), Nasrollahzadeh et al. (2018)
	Capacity and allocation	Day et al. (2012), Dobson et al. (2012), Rath et al. (2017)
	Division of labour	Batt and Terwiesch (2017), Best et al. (2015), Clark and Huckman (2012), Dobson et al. (2009), Jiang and Sodhi (2019), KC and Terwiesch (2011), Miedaner and Sülz (2019), Song et al. (2015), White et al. (2017)
	Teaching status	Theokary and Ren (2011)
Physician behavior	Multitasking	KC (2014)
	Absenteeism	Green et al. (2013), Wang and Gupta (2014)
	Productivity	Avgerinos and Gökpınar (2017), Tucker and Singer (2015) Song et al. (2018)
	Workload	Freeman et al. (2017), Berry Jaeker and Tucker (2017), KC and Terwiesch (2009), Kuntz and Scholtes (2015), Powell et al. (2012)
	Experience	Avgerinos and Gökpınar (2018), KC and Staats (2012), KC et al. (2013), Ramdas et al. (2018)
	Discretion	Baron et al. (2017), Chen et al. (2019b), Dai et al. (2017), Dobson et al. (2013), Ibanez et al. (2018), Tucker (2016), Wang et al. (2019d)
	Effect of technology	Bavafa et al. (2018), Bhargava and Mishra (2014), Rajan et al. (2019)
Medical decision making		Ayer et al. (2012), Helm et al. (2015), Laker et al. (2018)
Process management		Chandrasekaran et al. (2012), Foster et al. (2018), Senot et al. (2016a,b)

Table 3.A.5 Health Services SCs: Reimbursement SCs

Key Research Areas	Literature
Fee-for-service vs. bundled payment	Adida et al. (2017), Guo et al. (2019)
Bundled payment	Gupta and Mehrotra (2015)
Policy	Andritsos and Aflaki (2015), Aswani et al. (2019), Ata et al. (2013), Chen et al. (2015), Qian et al. (2017), Webb and Mills (2019)
Performance-based contracting	Adida and Bravo (2019), Andritsos (2018), Bastani et al. (2019), Ghamat et al. (2018), Jiang et al. (2012, 2020), Lee and Zenios (2012), Savva et al. (2019), Zhang et al. (2016)
Copayment	King et al. (2019)

Table 3.A.6 Health Services SCs: Supplies and equipment SCs

Key Research Areas	Literature
Supplies	See Kim and Kwon (2015) for a literature review
Deployment	Chan et al. (2016, 2018)
Maintenance and repair	Chan et al. (2019b)
Recalls	Mukherjee and Sinha (2018), Thirumalai and Sinha (2011)
Facilities/equipment planning	Cho et al. (2014)

Table 3.A.7 Pharmaceutical SCs: Innovation and R&D SCs

Key Research Areas	Literature
Clinical trials	Bertsimas et al. (2019), Fleischhacker et al. (2015) Kouvelis et al. (2017)
Biotechnology and pharmaceutical contracting	Bhattacharya et al. (2015), Savva and Scholtes (2014) Taneri and De Meyer (2017), Xiao and Xu (2012)
Co-location	Gray et al. (2015)
Drug surveillance	Goh et al. (2015)

Table 3.A.8 Pharmaceutical SCs: Manufacturing and distribution SCs

Key Research Areas	Literature
Contracting	Zhang et al. (2011), Zhao et al. (2012)
Role of intermediaries	Hu and Schwarz (2011), Hu et al. (2012), Kouvelis et al. (2015, 2018), Saha et al. (2019)
Shortages	Jia and Zhao (2017)
Forecasting	Stonebraker and Keefer (2009)
Product decisions	Altug and Sahin (2019), Fruchter and Mantrala (2010), Martagan et al. (2018, 2019), Stonebraker (2013)
Inventory	Bandi et al. (2019a)

Table 3.A.9 Special health services SCs: Blood SCs

Key Research Areas	Literature
Inventory	Paul et al. (2019), Sarhangian et al. (2018), Zhou et al. (2011)
Collection	Ayer et al. (2019b), Chen et al. (2019a)
Screening	El-Amine et al. (2018)

Table 3.A.10 Special health services SCs: Organ transplantation SCs

Key Research Areas	Literature
Allocation	Akan et al. (2012), Arıkan et al. (2018), Bandi et al. (2019b), Bertsimas et al. (2013), Dai et al. (2019), Kong et al. (2010)
Kidney exchange	Anderson et al. (2017), Ashlagi et al. (2019), Dickerson et al. (2019), Ding et al. (2018), Glorie et al. (2014)
Screening	Sabouri et al. (2017)
Listing	Ata et al. (2017), Gardner et al. (2017)
Capacity planning	Gökalp et al. (2019)
Recovery	Arora and Subramanian (2019)

Table 3.A.11 Special health services SCs: Vaccines SCs

Key Research Areas	Literature
Modeling influenza	Ekici et al. (2014), Long et al. (2018)
Contracting	Chick et al. (2017), Cho and Tang (2013), Dai et al. (2016)
Composition	Cho (2010), Özaltın et al. (2011)
Supply and demand mismatch	Adbi et al. (2019), Arifoğlu et al. (2012), Deo and Corbett (2010)
Policy	Duijzer et al. (2009), Mamani et al. (2013), Sun et al. (2009), Tebbens and Thompson (2009), Yamin and Gavious (2013)
Scheduling	Engineer et al. (2009)

Table 3.A.12 Health humanitarian SCs

Key Research Areas	Literature
Prioritization and distribution	Chan et al. (2013), Jacobson et al. (2012), Mills et al. (2018), Sun et al. (2018)
Resource-limited settings	Cevik et al. (2018), Deo and Sohoni (2015), Jónasson et al. (2017), Khademi et al. (2015), McCoy and Lee (2014)
Availability and affordability	Cherkesly et al. (2019), Gallien et al. (2017), Kazaz et al. (2016), Kohnke et al. (2017), Parvin et al. (2018), Taylor and Xiao (2014)
Allocation	Atasu et al. (2017), Natarajan and Swaminathan (2017)
Inventory	Natarajan and Swaminathan (2014)
Capacity	McCoy and Johnson (2014), Ramirez-Nafarrate et al. (2015)

3.B Challenges in Healthcare Delivery

Similar to traditional SCs, challenges such as variability, inflexibility, and waste (Cachon and Terwiesch 2009) are commonly observed in hSCs, making the management of these supply chains taxing. In addition, compared to SCs in other ecosystems, management of hSCs sometimes presents unique difficulties. In Section 3.B.1, we give an overview of the main clinical and public health challenges. Section 3.B.2 outlines key operational challenges in hSCs, and in Section 3.B.3, we discuss financial challenges and the ways in which payment structures can lead to inefficiencies in the healthcare system. A summary of the challenges, their implications and opportunities can be found on Table 3.2 of the main paper.

3.B.1 Clinical and Public Health Challenges

Different patient characteristics (e.g., health status, comorbidities, demographics, and preferences), conditions (e.g., injuries, illnesses, disabilities and diseases) and situations (e.g., disease progression and the availability of resources) entail different clinical challenges. Although the array of such clinical considerations is vast, there are a few overarching areas practitioners pay particular attention to. One top priority in healthcare delivery is patient safety, arising from medicine's fundamental guiding principle of "*do no harm"*. Effectiveness of care (assessed through various clinician–reported and patient–reported measures), efficiency, equitability, timeliness of care, and patient experience are also key concerns (Institute of Medicine (US) Committee on Quality of Health Care in America 2001). However, several difficulties including clinical uncertainty, medical errors, and the co–productive nature of healthcare threaten the delivery of these priorities. While we will broadly discuss some of these challenges in this section, we wish to emphasize the fact that more informed and detailed discussions are best left to healthcare experts and practitioners.

One major difficulty is uncertainty, which is to some degree is inherent in most aspects of healthcare delivery. Uncertainty can complicate and introduce variation in clinical decision

making, which is already a complicated endeavor because patients have distinct journeys in which care plans may change at each encounter. As Eddy (1984) notes in his paper on healthcare uncertainty, “Whether a physician is defining a disease, making a diagnosis, selecting a procedure, observing outcomes, assessing probabilities, assigning preferences, or putting it all together, he is walking on very slippery terrain." With the intent of providing a unified, coherent concept of uncertainty in healthcare, Han et al. (2011) propose a three–dimensional taxonomy characterizing uncertainty by its fundamental sources, issues, and locus. The authors point to probability (a phenomenon's indeterminacy), ambiguity (the lack of credible, reliable, or adequate information regarding a phenomenon), and complexity (difficulty in comprehending a phenomenon) as sources of uncertainty. Uncertainty can cause scientific (disease–centered uncertainties regarding diagnosis, prognosis, treatment, etc.), practical (system–centered uncertainties concerning the structures and processes of care), and personal (patient–centered psycho–social and existential uncertainties) issues. Lastly, this taxonomy describes uncertainty by its locus (existing in the minds of patients, clinicians, both, or neither). Such efforts at understanding and classifying uncertainty are building the groundwork for effective uncertainty management strategies, which are very much needed given the ongoing challenge of operating in an uncertain environment.

Medical errors, which are preventable acts encompassing preventive, diagnostic, and surgical care and treatment as well as device, equipment, and communication errors or failures, may result in unintended consequences (e.g., adverse effects) for the patient. They can occur as a result of actions not taken or as a result of the wrong actions taken (Rodziewicz and Hipskind 2019), and they pose a challenge for healthcare as they carry significant human, societal, and cost burdens. It is important to note that the incidence of medical errors can be mitigated by various operational strategies and safeguards, such as the standardization of procedures (Ramdas et al. 2018).

Another clinical challenge stems from the co–productive nature of healthcare (Andritsos 2018). Achieving safe and effective care depends on the efforts of both providers and patients. For instance, poor patient adherence can compromise the treatment efforts of providers and jeopardize safety and health outcomes. Improving patient engagement and provider receptiveness of patient preferences, as well as, bolstering more effective communication between patients and providers, could create an opportunity to deliver better care.

While the healthcare sector is focused on the treatment of disease in individuals, it simultaneously plays a central role in the domain of public health. Public health focuses on measures related to the prevention (reducing the incidence of ill health), protection (preventing the spread of communicable disease), and promotion (enabling people to lead healthier lifestyles) of health (Royal College of Nursing 2020). A closely related approach, population health, aims to improve health outcomes and reduce health inequalities across an entire population by addressing social, cultural, political, economic, commercial, and environmental determinants of health (Buck et al. 2018, Lovell and Bibby 2018). An aging population, rising prevalence of chronic disease, and widening health inequalities (e.g., women living in the most–deprived 10% of areas of England are expected to live for nine fewer years than those from the least–deprived 10% and spend nineteen fewer years in good health (Buck et al. 2018)) highlight the need for effective joint functioning of healthcare delivery and public health.

A healthy population has clear economic and societal benefits. However, the main challenge associated with public health is the trade–off between investment in upstream public health interventions associated with longer, healthier lives and spending for downstream short–term needs related to the treatment of disease (Marshall et al. 2018, Finch et al. 2018). Although many factors that contribute to non–communicable disease are behavioral and therefore preventable (e.g., smoking contributes to heart and lung disease), only a small fraction of health spending (3% in OECD countries) goes towards preventive services (Gmeinder et al. 2017). One likely explanation for this discrepancy stems from the fact that while healthcare interventions offer clear evidence of their efficacy, evidence of the impact of public health intervention is limited (Finch et al. 2018).

The intrinsic complexity of population health poses further challenges in the design of effective systems and interventions. Population health is influenced by many health and socioeconomic factors, and there can also be a multidirectional and dynamic relationship between those factors. For example, a child in good health may have a higher education potential, which results in good employment; in turn, employment and financial resources are important for good health (Marshall et al. 2018). Moreover, the effects of public health initiatives may take many years to become

apparent, and interventions that affect one individual directly may have spillover effects on others, such as family members (Finch et al. 2018, Marshall et al. 2018). Studying the public health component of healthcare ecosystems would create an opportunity to deliver care at a lower cost and would lead to a better understanding and more accurate characterizations of the longer–term outcomes of care delivery.

3.B.2 Operational Challenges

Healthcare services are characterized by a patient–provider–payer triad (Figure 3.B.1). Consequentially, there are two major differences between a traditional SC and an hSC: an hSC involves *delegated decision–making* and *third–party financing*. These differences are leading to the first two of the five major operational challenges we describe in this section.

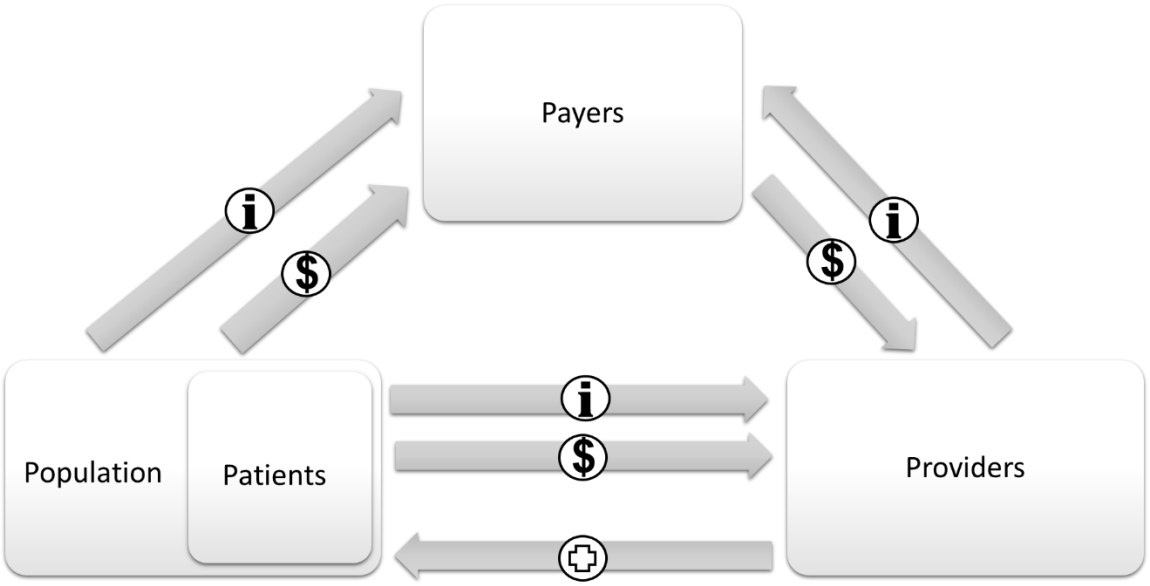

Figure 3.B.1 The patient–provider–payer triad of healthcare. Information (**i**), finances (**$**), and healthcare services (✚) flow between entities.

First, given the co–productive nature of healthcare, patients, as the consumer of healthcare services, should ideally be partners in designing their care processes. Yet, patients most often do not make consumption decisions themselves. Instead, they delegate these decisions to care

providers (e.g., doctors and nurses), who provide them with healthcare and make the “purchasing decisions" for them as a third–party agent. Second, in a traditional SC, the consumer pays for a given good or service. The value of the product or service can therefore usually be easily defined and measured. However, in an hSC, patients rarely pay the full price themselves. Further complicating matters, the providers are similarly “insulated from the price of the product or service" (wikipedia.com/health economics). It is the payers (e.g., insurance providers, employers, and/or the government) who largely provide reimbursement for the products and services charged by providers. Yet, the payers act with limited information, that is, without the full knowledge of patients' needs and demands (as payers are not fully privy to patients' health status, leading to adverse selection or hidden information) or of the benefits of the services provided (as payers are not fully privy to providers' actions, leading to moral hazard or hidden action).

The third challenge is partially caused by *information asymmetries* and further convoluted by the *power imbalances* in healthcare. Healthcare end consumers often have complicated needs and vulnerabilities. Yet because these patients' complex needs require expert services, patients are rarely in a position where they have complete information or the requisite knowledge to assess the quality of the service they receive[1]; this gives rise to additional information asymmetries in the triadic relationship. Furthermore, patients' vulnerabilities create a paternalistic care environment leading to potential power imbalances. Together, these matters make it difficult to meet consumers' needs and make it especially arduous to match demand with supply.

Efficient and effective SCM necessitates a clear understanding of performance measures pertaining to costs, outcomes, and quality. In healthcare, it is *challenging to quantify such performance measures,* which leads us to our fourth operational challenge. Often, accurate patient–level cost information is lacking due to inaccurate and often opaque cost allocations (Kaplan and Porter 2011).

Moreover, healthcare end consumers find it difficult to assess the value or utility of the service they receive–partially due to information asymmetries (as discussed above), partially due to the

[1] Healthcare is a credence good; in other words, it is “a type of good with qualities that cannot be observed by the consumer after purchase, making it difficult to assess its utility" (investopedia.com). Other examples of credence goods include expert services such as consulting and automobile repairs.

fact that healthcare is a merit good[2], and partially due to the fact that the health of a human being is at stake and healthcare can therefore be a sensitive subject. It is thus challenging to identify quality measures that are meaningful for physicians and patients alike. Simply put, physicians and patients may hold very different views regarding the degree to which a provided healthcare service led to a "good" result.

Such ambiguous or disparate valuations of healthcare services jeopardize the consumer focus of hSCM. Since, according to the World Health Organization Constitution (1946), "the highest attainable standard of health" is a fundamental right of every human being (World Health Organization 2017), there are ethical concerns and thus constraints on the levers that an SC manager can use in the context of an hSC. For example, emergency departments cannot deny emergency service to any patient, independent of their insurance coverage status. In addition, since healthcare is a social good, its value extends beyond the return to shareholders, and evaluating the impact of healthcare on society as a whole further complicates the quantification of its value.

Finally, effective SCM necessitates capability alignment and (end–to–end) goal optimization across all of the organizations in an SC. Yet one of the most prominent challenges in hSCs is the *pervasiveness of fragmented care*, which results in an unrealized value in care delivery. Fragmented hSCs are burdened with wastes such as duplicative and non–value adding functions and inefficiencies caused by supply–driven demand (Burns et al. 2002). Siloed care is costly, and it leads to sub–optimal patient safety and experience (Elhauge 2010, Jha et al. 2009, Stremikis et al. 2011). End–to–end goals are commonly achieved through information sharing and incentive and payment mechanisms. Yet within hSCs, "information on the value or cost added at each link is severely lacking…[making] meaningful knowledge sharing…impossible" (Burns et al. 2002). Despite the wide availability of healthcare IT systems, data integration in healthcare is limited and adoption of end–to–end applications is low. Therefore, fragmentation is a considerable impediment to SCM in healthcare systems.

[2] A merit good is "a type of good which, when consumed, provides external benefits, although these may not be fully recognized" (economicsonline.co.uk). Education is another example of a merit good.

3.B.3 Financial Challenges

The operational challenges discussed in Section 3.B.2 complicate the development of practical and effective payment mechanisms in healthcare. Table 3.3 in the main paper displays commonly used reimbursement methods and the main criticisms of each method. One very common method is fee–for–service (FFS) reimbursement. Because providers are paid per service provided, FFS has been heavily criticized for incentivizing providers to overtreat, overconsult, overdiagnose and overprescribe– all leading to mismatches between true patient needs and generated demand. Christensen et al. (2017) suggest FFS schemes should only be employed in "solution shops," where resources and processes are structured to diagnose and arrive at solutions for complicated and ambiguous medical problems.

In contrast to retrospective FFS schemes, prospective bundled payments have been introduced to curtail overtreatment and wasted resources. Yet, bundled payment may lead to other types of market failures, namely the underuse of services and upcoding. To overcome these limitations, Christensen et al. (2017) recommend the use of outcome–based reimbursement schemes in situations where treatments are standardized and are carried out following a definitive diagnosis (e.g., cataract surgeries). Similarly, value–based (Porter 2009) reimbursements have been developed to improve clinical quality by focusing on outcomes as well as costs. Although in comparison to fixed rate payment methods like FFS, outcome– and value–based reimbursement schemes have the potential to facilitate more patient–centric healthcare, they are more difficult to implement. Outcomes and costs need to be clearly defined and agreed upon; subsequently, they need to be objectively and comprehensively measured and reported in a timely manner. (It is possible, however, that the burden of data collection and measurement may diminish over time with the advancement and adoption of health technologies such as wearable devices.)

Payment methods can incentivize or disincentivize patients as well as providers. For instance, researchers have studied the effect of cost–sharing on patient actions, such as adherence to medication (Doshi et al. 2009, Maciejewski et al. 2010) and care utilization (Trivedi et al. 2010, Lambregts and van Vliet 2018). Upon analyzing and evaluating payment methods, several key considerations emerge. A critical line of inquiry should address whether payment methods carry

the right incentives for care providers and patients. Moreover, policy makers and managers should ensure that payment methods are properly matched with suitable care models. Relevant stakeholders should also establish whether they have the means (e.g., data availability) to successfully implement new reimbursement schemes.

References

Adbi, A., C. Chatterjee, M. Drev, A. Mishra. 2019. When the big one came: A natural experiment on demand shock and market structure in India's Influenza vaccine markets. *Production and Operations Research* 28(4):810–832.

Adida, E., F. Bravo. 2019. Contracts for healthcare referral services: Coordination via outcome–based penalty contracts. *Management Science* 65(3):1322–1341.

Adida, E., H. Mamani, S. Nassiri. 2017. Bundled payment vs. fee–for–service: Impact of payment scheme on performance. *Management Science* 63(5):1606–1624.

Akan, M., O. Alagoz, B. Ata, F.S. Erenay, A. Said. 2012. A broader view of designing the liver allocation system. *Operations Research* 60(4):757–770.

Allon, G., S. Deo, W. Lin. 2013. The impact of size and occupancy of hospital on the extent of ambulance diversion: Theory and evidence. *Operations Research* 61(3):544–562.

Altug, M.S., O. Sahin. 2019. Impact of parallel imports on pricing and product launch decisions in pharmaceutical industry. *Production and Operations Management* 28(2):258–275.

Anderson, D., G. Gao, B. Golden. 2014. Life is all about timing: An examination of differences in treatment quality for trauma patients based on hospital arrival time. *Production and Operations Management* 23(12):2178–2190.

Anderson, R., I. Ashlagi, D. Gamarnik, Y. Kanoria. 2017. Efficient dynamic barter exchange. *Operations Research* 65(6):1446–1459.

Andritsos, D.A. 2018. Incentive programs for reducing readmissions when patient care is co–produced. *Production and Operations Management* 27(6):999–1020.

Andritsos, D.A., S. Aaki. 2015. Competition and the operational performance of hospitals: The role of hospital objectives. *Production and Operations Management* 24(11):1812–1832.

Angst, C.M., S. Devaraj, C.C. Queenan. 2011. Performance effects related to the sequence of integration of healthcare technologies. *Production and Operations Management* 20(3):319–333.

Aprahamian, H., D.R. Bish, E.K. Bish. 2019. Optimal risk–based group testing. *Management Science* 65(9): 4365–4384.

Arifoğlu, K., S. Deo, S.M.R. Iravani. 2012. Consumption externality and yield uncertainty in the influenzavaccine supply chain: Interventions in demand and supply sides. *Management Science* 58(6):1072–1091.

Arıkan, M., B. Ata, J.J. Friedewald, R.P. Parker. 2018. Enhancing kidney supply through geographic sharing in the United States. Production and Operations Management 27(12):2103–2121.

Armony, M., C.W. Chan, B. Zhu. 2018. Critical care capacity management: Understanding the role of a step down unit. *Production and Operations Management* 27(5):859–883.

Arora, P., R. Subramanian. 2019. Improving societal outcomes in the organ donation value chain. *Production and Operations Management* 28(8):2110–2131.

Ashlagi, I., M. Burq, P. Jaillet, V. Manshadi. 2019. On matching and thickness in heterogeneous dynamic market. *Operations Research* 67(4):927–949.

Aswani, A., Z–J. M. Shen, A. Siddiq. 2019. Data–driven incentive design in the Medicare Shared Savings Program. *Operations Research* 67(4):1002–1026.

Ata, B., B.L. Killaly, T. Lennon Olsen, R.P. Parker. 2013. On hospice operations under Medicare reimbursement policies. *Management Science* 59(5):1027–1044.

Ata, B., A. Skaro, S. Tayur. 2017. OrganJet: Overcoming geographical disparities in access to deceased donor kidneys in the United States. *Management Science* 63(9):2776–2794.

Atasoy, H., P. Chen, K. Ganju. 2018. The spillover effects of health IT investments on regional healthcare costs. *Management Science* 64(6) 2515–2534.

Atasu, A., B. Toktay, W.M. Yeo, C. Zhang. 2017. Effective medical surplus recovery. Production and *Operations Research* 26(6):1142–1162.

Avgerinos, E., B. Gokpinar. 2017. Team familiarity and productivity in cardiac surgery operations: The effect of dispersion, bottlenecks, and task complexity. *Manufacturing & Service Operations Management* 19(1):19–35.

Avgerinos, E., B. Gokpinar. 2018. Task variety in professional service work: When it helps and when it hurts. *Production and Operations Management* 27(7):1368–1389.

Ayer, T., O. Alagoz, N.K. Stout. 2012. OR formula POMDP approach to personalize mammography screening decisions. *Operations Research 60*(5):1019–1034.

Ayer, T., O. Alagoz, N.K. Stout, E.S. Burnside. 2016. Heterogeneity in women's adherence and its role in optimal breast cancer screening policies. *Management Science* 62(5):1339–1362.

Ayer, T., C. Zhang, A. Bonifonte, A.C. Spaulding, J. Chhatwal. 2019a. Prioritizing hepatitis C treatment in U.S. prisons. *Operations Research* 67(3):853–873.

Ayer, T., C. Zhang, C. Zeng, C.C. White III, V.R. Joseph. 2019b. Analysis and improvement of blood collection operations. *Manufacturing & Service Operations Management 21*(1):29–46.

Ayvaci, M.U.S., O. Alagoz, E.S. Burnside. 2012. The effect of budgetary restrictions on breast cancer diagnostic decisions. *Manufacturing & Service Operations Management 14*(4):600–617.

Bandi, C., E. Han, O. Nohadani. 2019a. Sustainable inventory with robust periodic–affine policies and application to medical supply chains. *Management Science* 65(10):4636–4655.

Bandi, C., N. Trichakis, P. Vayanos. 2019b. Robust multiclass queuing theory for wait time estimation in resource allocation systems. *Management Science* 65(1):152–187.

Baron, O., O. Berman, D. Krass, J. Wang. 2017. Strategic idleness and dynamic scheduling in an open shop service network: Case study and analysis. *Manufacturing & Service Operations Management* 19(1):52–71.

Barz, C., K. Rajaram. 2015. Elective patient admission and scheduling under multiple resource constraints. *Production and Operations Management* 24(12):1907–1930.

Bastani, H., J. Goh, M. Bayati. 2019. Evidence of upcoding in pay–for–performance programs. *Management Science* 65(3):1042–1060.

Batt, R.J., C. Terwiesch. 2015. Waiting patiently: An empirical study of queue abandonment in an emergency department. *Management Science* 61(1):39–59.

Batt, R.J., C. Terwiesch. 2017. Early task initiation and other load–adaptive mechanisms in the emergency department. *Management Science* 63(11):3531–3551.

Bavafa, H., L.M. Hitt, C. Terwiesch. 2018. The impact of e–visits on visit frequencies and patient health: Evidence from primary care. *Management Science* 64(12):5461–5480.

Bavafa, H., S. Savin, C. Terwiesch. 2019. Managing patient panels with non–physician providers. *Production and Operations Management* 28(6):1577–1593.

Berry Jaeker, J.A., A. Tucker. 2017. Past the point of speeding up: The negative effects of workload saturation on efficiency and patient severity. *Management Science* 63(4):1042–1062.

Bertsimas, D., V.F. Farias, N. Trichakis. 2013. Fairness, efficiency, and flexibility in organ allocation for kidney transplantation. *Operations Research* 61(1):73–87.

Bertsimas, D., N. Korolko, A.M. Weinstein. 2019. Covariate–adaptive optimization in online clinical trials. *Operations Research* 67(4):1150–1161.

Best, T.J., B. Sandıkçı, D.D. Eisenstein, D.O. Meltzer. 2015. Managing hospital inpatient bed capacity through partitioning care into focused wings. *Manufacturing & Service Operations Management* 17(2):157–176.

Betcheva, L., F. Erhun, H. Jiang. 2019. “Healthcare supply chains” in The Oxford Handbook of Supply Chain Management. Edited by T.Y. Choi, J.J. Li, D.S. Rogers, T. Schoenherr, and S.M. Wagner, Oxford University Press, New York.

Bhargava, H.K., A.N. Mishra. 2014. Electronic medical records and physician productivity: Evidence from panel data analysis. *Management Science* 60(10):2543–2562.

Bhattacharya, S., V. Gaba, S. Hasija. 2015. A comparison of milestone–based and buyout options contracts for coordinating R&D partnerships. *Management Science* 61(5):963–978.

Bretthauer, K.M., H.S. Heese, H. Pun, E. Coe. 2011. Blocking in healthcare operations: A new heuristic and an application. *Production and Operations Management* 20(3):375–391.

Buck, D., A. Baylis, D. Dougall, R. Robertson. 2018. A vision for population health: Towards a healthier future. *The King's Fund*, London, UK. Available at: https://www.kingsfund.org.uk/sites/defaut/files/2018–11/A\%20vision\%20for\%20population\%20health\%20online\%20version.pdf.

Burns, L.R., R.A. Degraaff, P.M. Danzon, J.R. Kimberly, W.L. Kissick, M.V. Pauly. 2002. *The Wharton School study of the health care value chain*. L.R. Burns, ed., The Healthcare Value Chain: Producers, Purchasers, and Providers. Wiley, New York, NY.

Cachon, G., C. Terwiesch. 2009. *Matching Supply with Demand: An Introduction to Operations Management*. McGraw–Hill, Singapore.

Cayirli, T., K.K. Yang, S.A. Quek. 2012. A universal appointment rule in the presence of no–shows and walk–ins. *Production and Operations Management* 21(4):682–697.

Cevik, M., T. Ayer, O. Alagoz, B.L. Sprague. 2018. Analysis of mammography screening policies under resource constraints. *Production and Operations Management* 27(5):949–972.

Chan, C.W., J. Dong, L.J. Green. 2017a. Queues with time–varying arrivals and inspections with applications to hospital discharge policies. *Operations Research* 65(2):469–495.

Chan, C.W., V.F. Farias, N. Bambos, G.J. Escobar. 2012. Optimizing intensive care unit discharge decisions with patient readmissions. *Operations Research* 60(6):1323–1341.

Chan, C.W., V.F. Farias, G.J. Escobar. 2017b. The impact of delays on service times in the intensive care unit. *Management Science* 63(7):2049–2072.

Chan, C.W., L. Green, S. Lekwijit, L. Lu, G. Escobar. 2019a. Assessing the impact of service level when customer needs are uncertain: An empirical investigation of hospital step–down units. *Management Science* 65(2):751–775.

Chan, C.W., L.V. Green, Y. Lu, N. Leahy, R. Yurt. 2013. Prioritizing burn–injured patients during a disaster. *Manufacturing & Service Operations Management* 15(2):170–190.

Chan, T.C.Y., D. Demirtas, R.H. Kwon. 2016. Optimizing the deployment of public access defibrillators. *Management Science* 62(12):3617–3636.

Chan, T.C.Y., Z–J.M. Shen, A. Siddiq. 2018. Robust de_brillator deployment under cardiac arrest location uncertainty via row–and–column generation. *Operations Research* 66(2):358–379.

Chan, T.H., F. de Véricourt, O. Besbes. 2019b. Contracting in medical equipment maintenance services: An empirical investigation. *Management Science* 65(3):1136–1150.

Chandrasekaran, A., C. Senot, K.K. Boyer. 2012. Process management impact on clinical and experiential quality: Managing tensions between safe and patient–centered healthcare. *Manufacturing & Service Operations Management* 14(4):548–566.

Chehrazi, N., L.E. Cipriano, E.A. Enns. 2019. Dynamics of drug resistance: Optimal control of an infectious disease. *Operations Research* 67(3):619–650.

Chen, H., Q. Qian, A. Zhang. 2015. Would allowing privately funded health care reduce public waiting time? Theory and empirical evidence from Canadian joint replacement surgery data. *Production and Operations Management* 24(4):605–618.Chen, Q., T. Ayer, J. Chhatwal. 2018. Optimal M–switch surveillance policies for liver cancer in a hepatitis C–infected population.

Chen, R.R., L.W. Robinson. 2014. Sequencing and scheduling appointments with potential call–in patients. *Production and Operations Management* 23(9):1522–1538.

Chen, S., Y. Li, W. Zhou. 2019a. Joint decisions for blood collection and platelet inventory control. *Production and Operations Management* 28(7):1674–1691.

Chen, W., C–L. Tseng, S–J. S. Yang. 2019b. Improving hand hygiene process compliance through process monitoring in healthcare. *Manufacturing & Service Operations Management* 22(4):669–682.

Cherkesly, M., M. Rancourt, K.R. Smilowitz. 2019. Community healthcare network in underserved areas: Design, mathematical models, and analysis. *Production and Operations Research* 28(7):1716–1734.

Chhatwal, J., O. Alagoz, E.S. Burnside. 2010. Optimal breast biopsy decision–making based on mammographic features and demographic factors. *Operations Research* 58(6):1577–1591.

Chick, S.E., S. Hasija, J. Nasiry. 2017. Information elicitation and influenza vaccine production. *Operations Research* 65(1):75–96.

Cho, S–H. 2010. The optimal composition of influenza vaccines subject to random production yields. *Manufacturing & Service Operations Management* 12(2):256–277.

Cho, S–H., H. Jang, T. Lee, J. Turner. 2014. Simultaneous location of trauma centers and helicopters for emergency medical service planning. *Operations Research* 62(4):751–771.

Cho, S–H., C.S. Tang. 2013. Advance selling in a supply chain under uncertain supply and demand. *Manufacturing & Service Operations Management* 15(2):305–319.

Cho, S–H., H. Zhao. 2018. Healthcare supply chain. T. Dai, S. Tayur, eds., *Handbook of Healthcare Analytics: Theoretical Minimum for Conducting 21st Century Research on Healthcare Operations*. Wiley, New York, NY.

Chong, K.C., S.G. Henderson, M.E. Lewis. 2016. The vehicle mix decision in emergency medical service systems. *Manufacturing & Service Operations Management 18*(3):347–360.

Chow, V.S., M.L. Puterman, N. Salehirad, D. Atkins. 2011. Reducing surgical ward congestion through improved surgical scheduling and uncapacitated simulation. *Production and Operations Management* 20(3):418–430.

Christensen, C.M., J.H. Grossman, J. Huang. 2017. *The Innovator's Prescription: A Disruptive Solution for Health Care*. McGraw Hill Education, New York, NY.

Clark, J.R., R.S. Huckman. 2012. Broadening focus: Spillovers, complementarities, and specialization in the hospital industry. *Management Science* 58(4):708–722.

Dai, J.G., P. Shi. 2019. Inpatient overflow: An approximate dynamic programming approach. *Manufacturing & Service Operations Management* 21(4):894–911.

Dai, T., M. Akan, S. Tayur. 2017. Imaging room and beyond: The underlying economics behind physicians' test–ordering behavior in outpatient services. *Manufacturing & Service Operations Management* 19(1):99–113.

Dai, T., S–H. Cho, F. Zhang. 2016. Contracting for on–time delivery in the U.S. influenza vaccine supply chain. *Manufacturing & Service Operations Management* 18(3):332–346.

Dai, T., R. Zheng, K. Sycara. 2019. Jumping the line, charitably: Analysis and remedy of donor–priority rule. *Management Science* 66(2):622–641.

Day, R., R. Garfinkel, S. Thompson. 2012. Integrated block sharing: A win–win strategy for hospitals and surgeons. *Manufacturing & Service Operations Management* 14(4):567–583.

de Véricourt, F., O.B. Jennings. 2011. Nurse staffing in medical units: A queueing perspective. *Operations Research* 59(6):1320–1331.

de Vries, J., R. Huijsman. 2011. Supply chain management in health services: An overview. *Supply Chain Management: An International Journal 16*(3):159–165.

Deglise–Hawkinson, J., J.E. Helm, T. Huschka, D.L. Kaufman, M.P. Van Oyen. 2018. A capacity allocation planning model for integrated care and access management. *Production and Operations Management* 27(12):2270–2290.

Denton, B.T., A.J. Miller, H.J. Balasubramanian, T.R. Huschka. 2010. Optimal allocation of surgery blocks to operating rooms under uncertainty. *Operations Research* 58(4):802–816.

Deo, S., C.J. Corbett. 2010. Cournot competition under yield uncertainty: The case of the U.S. influenza vaccine market. *Manufacturing & Service Operations Management* 11(4):563–576.

Deo, S., I. Gurvich. 2011. Centralized vs. decentralized ambulance diversion: A network perspective. *Management Science* 57(1):1300–1319.

Deo, S., S. Iravani, T. Jiang, K. Smilowitz, S. Samuelson. 2013. Improving health outcomes through better capacity allocation in a community–based chronic care model. *Operations Research* 61(6):1277–1294.

Deo, S., K. Rajaram, S. Rath, U.S. Karmarkar, M.B. Goetz. 2015. Planning for HIV screening, testing, and care at the veteran's health administration. *Operations Research* 63(2):287–304.

Deo, S., M. Sohoni. 2015. Optimal decentralization of early infant diagnosis of HIV in resource–limited settings. *Manufacturing & Service Operations Management* 17(2):191–207.

Diamant, A., J. Milner, F. Quereshy. 2018. Dynamic patient scheduling for multi–appointment health care programs. *Production and Operations Management* 27(1):58–79.

Dickerson, J.P., A.D. Procaccia, T. Sandholm. 2019. Failure–aware kidney exchange. *Management Science* 65(4):1768–1791.

Ding, Y., D. Ge, S. He, C.T. Ryan. 2018. A nonasymptotic approach to analyzing kidney exchange graphs. *Operations Research* 66(4):918–935.

Ding, Y., E. Park, M. Nagarajan, E. Grafstein. 2019. Patient prioritization in emergency department triage systems: An empirical study of the Canadian Triage and Acuity Scale (CTAS). *Manufacturing & Service Operations Management* 21(4):723–741.

Dobson, G., S. Hasija, E.J. Pinker. 2011. Reserving capacity for urgent patients in primary care. *Production and Operations Management* 20(3):456–473.

Dobson, G., H–H. Lee, E. Pinker. 2010. A model of ICU bumping. *Operations Research* 58(6):1564–1576.

Dobson, G., H–H. Lee, A. Sainathan, V. Tilson. 2012. A queueing model to evaluate the impact of patient "batching" on throughput and ow time in a medical teaching facility. *Manufacturing & Service Operations Management* 14(4):584–599.

Dobson, G., E. Pinker, R.L. Van Horn. 2009. Division of labor in medical office practices. *Manufacturing & Service Operations Management* 11(3):525–537.

Dobson, G., T. Tezcan, V. Tilson. 2013. Optimal workflow decisions for investigators in systems with interruptions. *Management Science* 59(5):1125–1141.

Dong, J., E. Yom–Tov, G.B. Yom–Tov. 2019. The impact of delay announcements on hospital network coordination and waiting times. *Management Science* 65(5):1969–1994.

Doshi, J.A., J. Zhu, B.Y. Lee, S.E. Kimmel, K.G. Volpp. 2009. Impact of a prescription copayment increase on lipid–lowering medication adherence in veterans. *Circulation* 119:390–387.

Duijzer, L.E., W.L. van Jaarsveld, J. Wallinga, R. Dekker. 2009. Dose–optimal vaccine allocation over multiple populations. *Production and Operations Research* 27(1):143–159.

Eddy, D.M. 1984. Variations in physician practice: The role of uncertainty. *Health Affairs* 3(2):74–89.

Ekici, A., P. Keskinocak, J.L. Swann. 2014. Modeling influenza pandemic and planning food distribution. *Manufacturing & Service Operations Management* 16(1):11–27.

El–Amine, H., E.K. Bish, D.R. Bish. 2018. Robust post donation blood screening under prevalence rate uncertainty. *Operations Research* 66(1):1–17.

Elhauge, E. 2010. *The Fragmentation of U.S. Health Care: Causes and Solutions*. Oxford University Press, New York, NY.

Engineer, F.G., P. Keskinocak, L.K. Pickering. 2009. OR practice – catch–up scheduling for childhood vaccination. *Operations Research* 57(6):1307–1319.

Erenay, F.S., O. Alagoz, A. Said. 2014. Optimizing colonoscopy screening for colorectal cancer prevention and surveillance. *Manufacturing & Service Operations Management* 16(3):381–400.

Feldman, J., N. Liu, H. Topaloglu, S. Ziya. 2014. Appointment scheduling under patient preference and no–show behavior. Operations Research 62(4):794–811.

Finch, D., J. Bibby, T. Elwell–Sutton. 2018. Briefing: Taking our Health for Granted: Plugging the Public Health Grant Funding Gap. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/upload/publications/2018/Taking\%20our\%20health\%20for\%20granted_for\%20web.pdf.

Fleischhacker, A., A. Ninh, Y. Zhao. 2015. Positioning inventory in clinical trial supply chains. *Production and Operations Management* 24(6):991–1011.

Foster, K., P. Penninti, J. Shang, S. Kekre, G.G. Hegde, A. Venkat. 2018. Leveraging big data to balance new key performance indicators in emergency physician management networks. *Production and Operations Management* 27(10):1795–1815.

Freeman, M., N. Savva, S. Scholtes. 2017. Gatekeepers at work: An empirical analysis of a maternity unit. *Management Science* 63(10):3147–3167.

Freeman, N., M. Zhao, S. Melouk, J. Mittenthal. 2019. The economics of overlapping surgeries. *Production and Operations Management* 0(0):1–24.

Fruchter, G.E., M.K. Mantrala. 2010. Proactive planning of the timing of a partial switch of a prescription to over–the–counter drug. *Production and Operations Management* 19(5):614–628.

Gallien, J., I. Rashkova, R. Atun, P. Yadav. 2017. National drug stockout risks and the global fund disbursement process for procurement. *Production and Operations Research* 26(6):997–1014.

Gardner, K., M. Harchol–Balter, A. Scheller–Wolf, M. Velednitsky, S. Zbarsky. 2017. Redundancy–D: The power of D choices for redundancy. *Operations Research* 65(4):1078–1094.

Ghamat, S., G.S. Zaric, H. Pun. 2018. Contracts to promote optimal use of optional diagnostic tests in cancer treatment. *Production and Operations Management* 27(12):2184–2200.

Glorie, K.M., J.J. van de Klundert, A.P.M. Wagelmans. 2014. Kidney exchange with long chains: An efficient pricing algorithm for clearing barter exchanges with branch–and price. *Manufacturing & Service Operations Management* 16(4):498–512.

Gmeinder, M., D. Morgan, M. Mueller. 2017. How much do OECD countries spend on prevention? Available at: https://dx.doi.org/10.1787/f19e803c–en.

Goh, J., M.V. Bjarnadóttir, M. Bayati, S.A. Zenios. 2015. Active post marketing drug surveillance for multiple adverse events. O*perations Research* 63(6):1528–1546.

Goh, J., J. Pfeffer, S.A. Zenios. 2016. The relationship between workplace stressors and mortality and healthcosts in the United States. *Management Science* 62(2):608–628.

Gökalp, E., N. Gülpınar, X.V. Doan. 2019. Capacity planning for networks of stem–cell donation centers under uncertainty. *Production and Operations Management* doi:10.1111/poms.13090.

Gray, J.V., E. Siemsen, G. Vasudeva. 2015. Colocation still matters: Conformance quality and the interdependence of R&D and manufacturing in the pharmaceutical industry. *Management Science* 61(11):2760–2781.

Green, L.V., S. Savin, N. Savva. 2013. "Nursevendor problem": Personnel staffing in the presence of endogenous absenteeism. *Management Science* 59(10):2237–2256.

Gul, S., B.T. Denton, J.W. Fowler, T. Huschka. 2011. Bi–criteria scheduling of surgical services for an outpatient procedure center. *Production and Operations Management* 20(3):406–417.

Güneş, E.D., E.L. Örmeci, D. Kunduzcu. 2014. Preventing and diagnosing colorectal cancer with a limited colonoscopy resource. *Production and Operations Management* 24(1):1–20.

Guo, P., C.S. Tang, Y. Wang, M. Zhao. 2019. The impact of reimbursement policy on social welfare, revisit rate, and waiting time in a public healthcare system: Fee–for–service versus bundled payment. *Manufacturing & Service Operations Management* 21(1):154–170.

Gupta, D., M. Mehrotra. 2015. Bundled payments for healthcare services: Proposer selection and information sharing. *Operations Research* 63(4):772–788.

Han, P.K., W.M. Klein, N.K. Arora. 2011. Varieties of uncertainty in health care: A conceptual taxonomy. *Medical Decision Making* 31(6):828–838.

Han, X., N. Yaraghi, R. Gopal. 2018. Winning at all costs: Analysis of inflation in nursing homes' rating system. *Production and Operations Management* 27(2):215–233.

He, B., F. Dexter, A. Macario, S. Zenios. 2012. The timing of staffing decisions in hospital operating rooms: Incorporating workload heterogeneity into the newsvendor problem. *Manufacturing & Service Operations Management* 14(1):99–114.

He, S., M. Sim, M. Zhang. 2019. Data–driven patient scheduling in emergency departments: A hybrid robust–stochastic approach. *Management Science* 65(9):4123–4140.

Helm, J.E., S. AhmadBeygi, M.P. Van Oyen. 2011. Design and analysis of hospital admission control for operational effectiveness. *Production and Operations Management* 20(3):359–374.

Helm, J.E., A. Alaeddini, J.M. Stauffer, K.M. Bretthauer, T.A. Skolarus. 2016. Reducing hospital readmissions by integrating empirical prediction with resource optimization. *Production and Operations Management* 25(2):233–257.

Helm, J.E., M.S. Lavieri, M.P. Van Oyen, J.D. Stein, D.C. Musch. 2015. Dynamic forecasting and control algorithms of glaucoma progression for clinician decision support. *Operations Research* 63(5):979–999.

Helm, J.E., M.P. Van Oyen. 2014. Design and optimization methods for elective hospital admissions. *Operations Research* 62(6):1265–1282.

Hu, Q., L.B. Schwarz. 2011. Controversial role of GPOs in healthcare–product supply chains. *Production and Operations Management* 20(1):1–15.

Hu, Q., L.B. Schwarz, N.A. Uhan. 2012. The impact of group purchasing organizations on healthcare–product supply chains. *Manufacturing & Service Operations Management* 14(1):7–23.

Hu, W., C.W. Chan, J.R. Zubizarreta, G.J. Escobar. 2018. An examination of early transfers to the ICU based on a physiologic risk score. *Manufacturing & Service Operations Management* 20(3):531–549.

Huang, J., B. Carmeli, A. Mandelbaum. 2015. Control of patient ow in emergency departments, or multiclass queues with deadlines and feedback. *Operations Research* 63(4):892–908.

Huh, W.T., N. Liu, V.A. Truong. 2013. Multiresource allocation scheduling in dynamic environments. *Manufacturing & Service Operations Management* 15(2):280–291.

Hydari, M.Z., R. Telang, W.M. Marella. 2019. Saving patient Ryan – Can advanced Electronic Medical Records make patient care safer? *Management Science* 65(5):2041–2059.

Ibanez, M.R., J.R. Clark, R.S. Huckman, B.R. Staats. 2018. Discretionary task ordering: Queue management in radiological services. *Management Science* 64(9):4389–4407.

Institute of Medicine (US) Committee on Quality of Health Care in America. 2001. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington (DC): National academies press (US).

Izady, N. 2015. Appointment capacity planning in specialty clinics: A queueing approach. Operations Research 63(4):916–930.

Izady, N., I. Mohamed. 2021. A clustered overflow configuration of inpatient beds in hospitals. *Manufacturing & Service Operations Management* 23(1):139–154.

Jacobson, E.U., N. Tanık Argon, S. Ziya. 2012. Priority assignment in emergency response. *Operations Research* 60(4):813–832.

Jha, A.K., D.C. Chan, A.B. Ridgway, C. Franz, D.W. Bates. 2009. Improving safety and eliminating redundant tests: Cutting costs in U.S. hospitals. *Health Affairs* 28(5):1475–1484.

Jia, J., H. Zhao. 2017. Mitigating the U.S. drug shortages through Pareto–improving contracts. *Production and Operations Management* 26(8):1463–1480.

Jiang, H., Z. Pang, S. Savin. 2012. Performance–based contracts for outpatient medical services. *Manufacturing & Service Operations Management* 14(4):654–669.

Jiang, H., Z. Pang, S. Savin. 2020. Performance incentives and competition in health care markets. *Production and Operations Management* 29(5):1145–1164.

Jiang, H., M.S. Sodhi. 2019. Analyzing the proposed reconfiguration of accident–and–emergency facilities in England. *Production and Operations Management* 28(7):1837–1857.

Jónasson, J.O., S. Deo, J. Gallien. 2017. Improving HIV early infant diagnosis supply chains in Sub Saharan Africa: Models and application to Mozambique. *Operations Research* 65(6):1479–1493.

Jung, K.S., M. Pinedo, C. Sriskandarajah, V. Tiwari. 2019. Scheduling elective surgeries with emergency patients at shared operating rooms. *Production and Operations Management* 28(6):1407–1430.

Kamali, M.F., T. Tezcan, O. Yildiz. 2019. When to use provider triage in emergency department. *Management Science 65*(3):1003–1019.

Kaplan, R.S., M.E. Porter. 2011. How to solve the cost crisis in health care. *Harvard Business Review* 89(9):46–52, 54, 56–61.

Kazaz, B., S. Webster, P. Yadav. 2016. Interventions for an artemisinin–based malaria medicine supply chain. *Production and Operations Research* 25(9):1576–1600.

KC, D.S. 2014. Does multitasking improve performance? Evidence from the emergency department. *Manufacturing & Service Operations Management* 16(2):168–183.

KC, D.S., B.R. Staats. 2012. Accumulating a portfolio of experience: The effect of focal and related experience on surgeon performance. *Manufacturing & Service Operations Management* 14(4):618–633.

KC, D.S., B.R. Staats, F. Gino. 2013. Learning from my success and from others' failure: Evidence from minimally invasive cardiac surgery. *Management Science* 59(11):2435–2449.

KC, D.S., C. Terwiesch. 2009. Impact of workload on service time and patient safety: An econometric analysis of hospital operations. *Management Science* 55(9):1486–1498.

KC, D.S., C. Terwiesch. 2011. The effects of focus on performance: Evidence from California hospitals. *Management Science* 57(11):1897–1912.

KC, D.S., C. Terwiesch. 2012. An econometric analysis of patient flows in the cardiac intensive care unit. *Manufacturing & Service Operations Management* 14(1):50–65.

KC, D.S., C. Terwiesch. 2017. Benefits of surgical smoothing and spare capacity: An econometric analysis of patient flow. *Production and Operations Management* 26(9):1663–1684.

Khademi, A., D.R. Saure, A.J. Schaefer, R.S. Braithwaite, M.S. Roberts. 2015. The price of nonabandonment: HIV in resource–limited settings. *Manufacturing & Service Operations Management* 17(4):554–570.

Kim, K., S. Mehrotra. 2015. A two–stage stochastic integer programming approach to integrated staffing and scheduling with application to nurse management. *Operations Research* 63(6):1431–1451.

Kim, S–H., C.W. Chan, M. Olivares, G. Escobar. 2015. ICU admission control: An empirical study of capacity allocation and its implication for patient outcomes. *Management Science* 61(1):19–38.

Kim, S.–H., I.–W.G. Kwon. 2015. The study of healthcare supply chain management in United States: Literature review. *Management Review: An International Journal* 10(2):34–56.

King, G.J., X. Chao, I. Duenyas. 2019. Who benefits when prescription drug manufacturers offer copay coupons? *Management Science* 65(8):3758–3775.

Kohnke, E.J., U.K. Mukherjee, K.K. Sinha. 2017. Delivering long–term surgical care in underserved communities: The enabling role of international NPOs as partners. *Production and Operations Research* 26(6):1092–1119.

Kong, N., A.J. Schaefer, B. Hunsaker, M.S. Roberts. 2010. Maximizing the efficiency of the U.S. liver allocation system through region design. *Management Science* 56(12):2111–2122.

Kouvelis, P., J. Milner, Z. Tian. 2017. Clinical trials for new drug development: Optimal investment and application. *Manufacturing & Service Operations Management* 19(3):437–452.

Kouvelis, P., Y. Xiao, N. Yang. 2015. PBM competition in pharmaceutical supply chain: Formulary design and drug pricing. *Manufacturing & Service Operations Management* 17(4):511–526.

Kouvelis, P., Y. Xiao, N. Yang. 2018. Drug pricing for competing pharmaceutical manufacturers distributing through a common PBM. *Production and Operations Management* 27(8):1399–1419.

Kucukyazici, B., V. Verter, N.E. Mayo. 2011. An analytical framework for designing community–based care for chronic diseases. *Production and Operations Management* 20(3):474–488.

Kuntz, L., S. Scholtes. 2015. Stress on the ward: Evidence of safety tipping points in hospitals. Management Science 61(4):754–771.

Kuntz, L., S. Scholtes, S. Sülz. 2019. Separate and concentrate: Accounting for patient complexity in general hospitals. *Management Science* 65(6):2482–2501.

LaGanga, L.R., S.R. Lawrence. 2012. Appointment overbooking in health care clinics to improve patient service and clinic performance. *Production and Operations Management* 21(5) 874–888.

Lahiri, A., A. Seidmann. 2012. Information hang–overs in healthcare service systems. Manufacturing & Service Operations Management 14(4):634–653.

Laker, L.F., C.M. Froehle, J.B. Windeler, C.J. Lindsell. 2018. Quality and efficiency of the clinical decision–making process: Information overload and emphasis framing. *Production and Operations Management* 27(12):2213–2225.

Lambregts, T.R., C.J.A. van Vliet. 2018. The impact of copayments on mental healthcare utilization: A natural experiment. *The European of Health Economics* 19(6):775–784.

Lee, D.K.K., S.A. Zenios. 2009. Optimal capacity overbooking for the regular treatment of chronic conditions. *Operations Research* 57(4):852–865.

Lee, D.K.K., S.A. Zenios. 2012. An evidence–based incentive system for Medicare's end–stage renal disease program. *Management Science* 58(6):1092–1105.

Lee, E., M.S. Lavieri, M. Volk. 2019. Optimal screening for hepatocellular carcinoma: A restless bandit model. *Manufacturing & Service Operations Management* 21(1):198–212.

Lee, S.J., G.R. Heim, C. Sriskandarajah, Y. Zhu. 2018. Outpatient appointment block scheduling under patient heterogeneity and patient no–shows. *Production and Operations Management* 27(1):28–48.

Lemay, B., A. Cohn, M. Epelman, S. Gorga. 2015. New methods for resolving conflicting requests with examples from medical residency scheduling. Production and *Operations Management* 26(9):1778–1793.

Li, Y., S.Y. Tang, J. Johnson, D.A. Lubarsky. 2019. Individualized no–show predictions: Effect on clinic overbooking and appointment reminders. *Production and Operations Management* 28(8):2068–2086.

Liu, J., J. Xie, K. Khiong Yang, Z. Zheng. 2019a. Effects of rescheduling on patient no–show behavior in outpatient clinics. *Manufacturing & Service Operations Management* 21(4):780–797.

Liu, N. 2016. Optimal choice for appointment scheduling window under patient no–show behavior. *Production and Operations Management* 25(1):128–142.

Liu, N., S.R. Finkelstein, M.E. Kruk, D. Rosenthal. 2019b. When waiting to see a doctor is less irritating: Understanding patient preferences and choice behavior in appointment schedulings. *Management Science* 64(5):1975–1996.

Liu, N., V–A. Truong, X. Wang, B.R. Anderson. 2019c. Integrated scheduling and capacity planning with considerations for patients' length–of–stays. *Production and Operations Management* 28(7):1735–1756.

Liu, N., S. Ziya. 2014. Panel size and overbooking decisions for appointment–based services under patient no–shows. *Production and Operations Management* 23(12):2209–2223.

Liu, N., S. Ziya, V.G. Kulkarni. 2010. Dynamic scheduling of outpatient appointments under patient no–shows and cancellations. *Manufacturing & Service Operations Management* 12(2):347–364.

Liu, X., M. Hu, J.E. Helm, M.S. Lavieri, T.A. Skolarus. 2018. Missed opportunities in preventing hospital readmissions: Redesigning post–discharge checkup policies. *Production and Operations Management* 27(12):2226–2250.

Long, E.F., K.S. Mathews. 2018. The boarding patient: Effects of ICU and hospital occupancy surges on patient flow. *Production and Operations Management* 27(12):2122–2143.

Long, E.F., E. Nohdurft, S. Spinler. 2018. Spatial resource allocation for emerging epidemics: A comparison of greedy, myopic, and dynamic policies. *Manufacturing & Service Operations Management* 20(2):181–198.

Lovell, N., J. Bibby. 2018. What Makes us Healthy? An Introduction to the Social Determinants of Health. *The Health Foundation*. Available at: https://www.health.org.uk/sites/default /files/What–makes–us–healthy–quick–guide.pdf.

Lu, L.X., S.F. Lu. 2017a. Distance, quality, or relationship? Interhospital transfer of heart attack patients. *Manufacturing & Service Operations Management* 27(12):2251–2269.

Lu, S.F., L.X. Lu. 2017b. Do mandatory overtime laws improve quality? Staffing decisions and operational flexibility of nursing homes. *Management Science* 63(11):3566–3585.

Lu, S.F., H. Rui, Seidmannm A. 2018. Does technology substitute for nurses? Staffing decisions in nursing homes. *Management Science* 64(4):1842–1859.

Luo, J., V.G. Kulkarni, S. Ziya. 2012. Appointment scheduling under patient no–shows and service interruptions. *Manufacturing & Service Operations Management* 14(4):670–684.

Maciejewski, M., J.F. Farley, J. Parker, D.Wansink. 2010. Copayment reductions generate greater medication adherence in targeted patients. *Health Affairs* 29(11):2002–2008.

Mamani, H., S. E. Chick, D. Simchi–Levi. 2013. A game–theoretic model of international influenza vaccination coordination. *Manufacturing & Service Operations Management* 59(7):1650–1670.

Mandelbaum, A., P. Momčilović, N. Trichakis, S. Kadish, R. Leib, C.A. Bunnell. 2019. Data–driven appointment–scheduling under uncertainty: The case of an infusion unit in a cancer center. *Management Science* 66(1):243–270.

Mandelbaum, A., P. Momčilović, Y. Tseytlin. 2012. On fair routing from emergency departments to hospital wards: QED queues with heterogeneous servers. *Management Science* 58(7):1273–1291.

Marshall, L., D. Finch, L. Cairncross, J. Bibby. 2018. Briefing: The Nation's Health as an Asset. *The Health Foundation.* Available at: https://www.health.org.uk/sites/default/files/upload/publications/ 2018/The\%20nation\%27s\%20health\%20as\%20an\%20asset.pdf.

Martagan, T., A. Krishnamurthy, P.A. Leland. 2020. Managing trade–offs in protein manufacturing: How much to waste? *Manufacturing & Service Operations* 22(2):330–345.

Martagan, T., A. Krishnamurthy, P.A. Leland, C.T. Maravelias. 2018. Performance guarantees and optimal purification decisions for engineered proteins. *Operations Research* 66(1):18–41.

McCoy, J.H., M.E. Johnson. 2014. Clinic capacity management: Planning treatment programs that incorporate adherence. *Production and Operations Research* 23(1):1–18.

McCoy, J.H., H.L. Lee. 2014. Using fairness models to improve equity in health delivery fleet management. *Production and Operations Research* 23(6):965–977.

McLay, L.A., M.E. Mayorga. 2013. A dispatching model for server–to–customer systems that balances efficiency and equity. *Manufacturing & Service Operations Management* 15(2):205–220.

Meng, F., F. Qi, M. Zhang, J. Ang, S. Chu, M. Sim. 2015. A robust optimization model for managing elective admission in a public hospital. *Operations Research* 63(6):1452–1467.

Miedaner, F., S. Sülz. 2019. Boundaries of focus and volume: An empirical study in neonatal intensive care. *Production and Operations Management* doi:https://doi.org/doi:10.1111/poms.13110.

Mills, A.F., N. TanıkArgon, S. Ziya. 2013. Resource–based patient prioritization in mass–casualty incident. *Manufacturing & Service Operations Management* 15(3):361–377.

Mills, A.F., N. Tanık Argon, S. Ziya. 2018. Dynamic distribution of patients to medical facilities in the aftermath of a disaster. *Operations Research* 66(3):716–732.

Mochon, D., J. Schwartz, J. Maroba, D. Patel, D. Ariely. 2017. Gain without pain: The extended effects of a behavioral health intervention. *Management Science* 63(1):58–72.

Mukherjee, U.K., K.K. Sinha. 2018. Product recall decisions in medical device supply chains: A big data analytic approach to evaluating judgment bias. *Production and Operations Management* 27(10): 1816–1833.

Nasrollahzadeh, A.A., A. Khademi, M.E. Mayorga. 2018. Real–time ambulance dispatching and relocation. *Manufacturing & Service Operations Management* 20(3):467–480.

Natarajan, K.V., J.M. Swaminathan. 2014. Inventory management in humanitarian operations: Impact of amount, schedule, and uncertainty in funding. *Manufacturing & Service Operations Management* 16(4):595–603.

Natarajan, K.V., J.M. Swaminathan. 2017. Multi–treatment inventory allocation in humanitarian health settings under funding constraints. *Production and Operations Research* 26(6):1015–1034.

Oh, J., Z. Zheng, I.R. Bardhan. 2018. Sooner or later? Health information technology, length of stay, and readmission risk. *Production and Operations Management* 27(11):2038–2053.

Örmeci, E.L., E.D. Güneş, D. Kunduzcu. 2016. A modeling framework for control of preventive services. *Manufacturing & Service Operations Management* 18(2):227–244.

Osadchiy, N., D.S. KC. 2017. Are patients patient? The role of time to appointment in patient flow. *Production and Operations Management* 26(3):469–490.

Özaltın, O.Y., O.A. Prokopyev, A.J. Schaefer, M.S. Roberts. 2011. Optimizing the societal benefits of the annual influenza vaccine: A stochastic programming approach. *Operations Research* 59(5): 1131–1143.

Ozen, A., Y. Marmor, T. Rohleder, H. Balasubramanian, J. Huddleston, P. Huddleston. 2016. Optimization and simulation of orthopedic spine surgery cases at Mayo Clinic. *Manufacturing & Service Operations Management* 18(1):157–175.

Parvin, H., S. Beygi, J.E. Helm, P.S. Larson, M.P. Van Oyen. 2018. Distribution of medication considering information, transshipment, and clustering: Malaria in Malawi. *Production and Operations Management* 27(4):1059–1478.

Patrick, J. 2011. Access to long–term care: The true cause of hospital congestion? *Production and Operations Management* 20(3):347–358.

Paul, A., T. Rajapakshe, S. Mallik. 2019. Socially optimal contracting between a regional blood bank and hospitals. *Production and Operations Management* 28(4):908–932.

Pierskalla, W.P. 2005. Supply chain management of blood banks. M.L. Brandeau, F. Sainfort, W.P. Pierskalla, eds., Operations Research and Health Care. *International Series in Operations Research & Management Science*, vol. 70. Springer, Boston, MA.

Pinker, E., T. Tezcan. 2013. Determining the optimal configuration of hospital inpatient rooms in the presence of isolation patients. *Operations Research* 61(6):1259–1276.

Porter, M.E. 2009. A strategy for health care reform toward a value–based system. *The New England Journal of Medicine* 361(2):109–112.

Powell, A., S. Savin, N. Savva. 2012. Physician workload and hospital reimbursement: Overworked physicians generate less revenue per patient. *Manufacturing & Service Operations Management* 14(4):512–528.

Price, C., B. Golden, M. Harrington, R. Konewko, E. Wasil, W. Herring. 2011. Reducing boarding in a post–anesthesia care unit. *Production and Operations Management* 20(3):431–441.

Qian, Q., P. Guo, R. Lindsey. 2017. Comparison of subsidy schemes for reducing waiting times in healthcare systems. *Production and Operations Management* 26(11):2033–2049.

Queenan, C., K. Cameron, A. Snell, J. Smalley, N. Joglekar. 2019. Patient heal thyself: Reducing hospital readmissions with technology–enabled continuity of care and patient activation. *Production and Operations Management* 0:1–13.

Rajan, B., T. Tezcan, A. Seidmann. 2019. Service systems with heterogeneous customers: Investigating the effect of telemedicine on chronic care. *Management Science* 65(3):1236–1267.

Ramdas, K., K. Saleh, S. Stern, H. Liu. 2018. Variety and experience: Learning and forgetting in the use of surgical devices. *Management Science* 64(6):2590–2608.

Ramirez–Nafarrate, A., J.D. Lyon, J.W. Fowler, O.M. Araz. 2015. Point–of–dispensing location and Capacity optimization via a decision support system. *Production and Operations Management 2* 4(8):1311–1328.

Rath, S., K. Rajaram, A. Mahajan. 2017. Integrated anesthesiologist and room scheduling for surgeries: Methodology and application. *Operations Research* 65(6):1460–1478.

Rauner, M.S., W.J. Gutjahr, K. Heidenberger, J. Wagner, J. Pasia. 2010. Dynamic policy modeling for chronic diseases: Metaheuristic–based identification of Pareto–optimal screening strategies. *Operations Research* 58(5):1269–1286.

Robinson, L.W., R.R. Chen. 2010. A comparison of traditional and open–access policies for appointment scheduling. Manufacturing & Service Operations Management 12(2):330–346.

Rodziewicz, T.L., J.E. Hipskind. 2019. Medical Error Prevention. *StatPearls*, Treasure Island, FL.

Roth, A., A.L. Tucker, S. Venkataraman, J. Chilingerian. 2019. Being on the productivity frontier: Identifying "triple aim performance" hospitals. *Production and Operations Management* 28(9): 2165–2183.

Royal College of Nursing. 2020. Public health. Available at: https://www.rcn.org.uk/clinical–topics/public–health.

Sabouri, A., W.T. Huh, S.M. Shechter. 2017. Screening strategies for patients on the kidney transplant waiting list. *Operations Research* 65(45):1131–1146.

Saghafian, S., W.J. Hopp, S.M.R. Iravani, Y. Cheng, D. Diermerier. 2019. Workload management in telemedical physician triage and other knowledge–based service systems. *Management Science* 64(11):5180–5197.

Saghafian, S., W.J. Hopp, M.P. Van Oyek, J.S. Desmond, S.L. Kronick. 2012. Patient streaming as a mechanism for improving responsiveness in emergency departments. *Operations Research* 60(5): 1080–1097.

Saghafian, S., W.J. Hopp, M.P. Van Oyen, J.S. Desmond, S.L. Kronick. 2014. Complexity–augmented triage: A tool for improving patient safety and operational efficiency. *Manufacturing & Service Operations Management* 16(3):329–345.

Saha, R.L., A. Seidmann, V. Tilson. 2019. The impact of custom contracting and the infomediary role of healthcare GPOs. *Production and Operations Management* 28(3):650–667.

Salzarulo, P.A., K.M. Bretthauer, M.J. Côté, K.L. Schultz. 2011. The impact of variability and patient information on health care system performance. Production and Operations Management 20(6): 848–859.

Salzarulo, P.A., S. Mahar, S. Modi. 2016. Beyond patient classification: Using individual patient characteristics in appointment scheduling. *Production and Operations Management* 25(6):1056–1072.

Samiedaluie, S., V. Kucukyazici, B. Verter, D. Zhang. 2017. Managing patient admissions in a neurology ward. *Operations Research* 65(3):635–656.

Samorani, M., S. Ganguly. 2016. Optimal sequencing of unpunctual patients in high–service–level clinics. *Production and Operations Management* 25(2):330–346.

Sarhangian, V., H. Abouee–Mehrizi, O. Baron, O. Berman. 2018. Threshold–based allocation policies for inventory management of red blood cells. *Manufacturing & Service Operations Management* 20(2):347–362.

Savva, N., S. Scholtes. 2014. Opt–out options in new product co–development partnerships. *Production and Operations Management* 23(8):1370–1386.

Savva, N., T. Tezcan, Ö. Yıldız. 2019. Can yardstick competition reduce waiting times? *Management Science* 65(7):3196–3215.

Senot, C. 2019. Continuity of care and risk of readmission: An investigation into the healthcare journey of heart failure patients. *Production and Operations Management* 28(8):2008–2030.

Senot, C., A. Chandrasekaran, P.T. Ward. 2016a. Role of bottom–up decision processes in improving the quality of health care delivery: A contingency perspective. *Production and Operations Management* 25(3):458–476.

Senot, C., A. Chandrasekaran, P.T. Ward, A.L. Tucker, S.D. Moffatt–Bruce. 2016b. The impact of combining conformance and experiential quality on hospitals' readmissions and cost performance. *Management Science* 62(3):829–848.

Sharma, L., C. Queenan, O. Ozturk. 2019. The impact of information technology and communication on medical malpractice lawsuits. *Production and Operations Management* 10(28):2552–2572.

Shi, P., M.C. Chou, J.G. Dai, D. Ding, J. Sim. 2016. Models and insights for hospital inpatient operations: Time dependent ED boarding time. *Management Science* 62(1):1–28.

Slaugh, V.W., A.A. Scheller–Wolf, S.R. Tayur. 2018. Consistent staffing for long–term care through on–call pools. *Production and Operations Management* 27(12):2144–2161.

Song, H., A. Tucker, K.L. Murrell. 2015. The diseconomies of queue pooling: An empirical investigation of emergency department length of stay. *Management Science* 61(12):3032–3053.

Song, H., A. Tucker, K.L. Murrell, D.R. Vinson. 2018. Closing the productivity gap: Improving worker productivity through public relative performance feedback and validation of best practices. *Management Science* 64(6):2628–2649.

Song, H., A.L. Tucker, R. Graue, S. Moravick, J.J. Yang. 2019. Capacity pooling in hospitals: The hidden consequences of off–service placement. *Management Science* Articles in Advance.

Stonebraker, J.S. 2013. Product–generation transition decision making for Bayer's hemophilia drugs: Global capacity expansion under uncertainty with supply–demand imbalances. *Operations Research* 61(5):1119–1133.

Stonebraker, J.S., D.L. Keefer. 2009. OR practice – modeling potential demand for supply constrained drugs: A new hemophilia drug at Bayer biological products. *Operations Research* 57(1):19–31.

Stremikis, K., C. Schoen, A–K. Fryer. 2011. A Call for Change: Commonwealth Fund 2011 Survey of Public Views of the U.S. Health System, vol. 6. *The Commonwealth Fund*: Issue Brief.

Sun, P., L. Yang, F. de Véricourt. 2009. Sel_sh drug allocation for containing an international influenza pandemic at the onset. *Operations Research* 57(6):1320–1332.

Sun, Z., N. Tanık Argon, S. Ziya. 2018. Patient triage and prioritization under austere conditions. *Management Science* 64(10):4471–4489.

Taneri, N., A. De Meyer. 2017. Contract theory: Impact on biopharmaceutical alliance structure and performance. *Manufacturing & Service Operations Management* 19(3):453–471.

Taylor, T.A., W. Xiao. 2014. Subsidizing the distribution channel: Donor funding to improve the availability of malaria drugs. *Management Science* 60(10):2461–2477.

Tebbens, R.J.D., K.M. Thompson. 2009. Priority shifting and the dynamics of managing eradicable infectious diseases. *Management Science* 55(4):650–663.

Theokary, C., Z.J. Ren. 2011. An empirical study of the relations between hospital volume, teaching status, and service quality. *Production and Operations Management* 20(3):303–318.

Thirumalai, S., K.K. Sinha. 2011. Product recalls in the medical device industry: An empirical exploration of the sources and _financial consequences. *Management Science* 57(2):376–392.

Thompson, S., M. Nunez, R. Gar_nkel, M.D. Dean. 2009. Efficient short–term allocation and reallocation of patients to floors of a hospital during demand surges. *Operations Research* 57(2):261–273.

Trivedi, A.N., H. Moloo, V. Mor. 2010. Increased ambulatory care copayments and hospitalizations among the elderly. *The New England Journal of Medicine* 362(4):320–328.

Tucker, A.L. 2016. The impact of workaround difficulty on frontline employees' response to operational failures: A laboratory experiment on medication administration. *Management Science* 62(4):1124–1144.

Tucker, A.L., S.J. Singer. 2015. The effectiveness of management–by–walking–around: A randomized field study. *Production and Operations Management* 24(2):253–271.

Wang, D., D. Morrice, K. Muthuraman, J.F. Bard, L.K. Leykum, S.H. Norrily. 2018. Coordinated scheduling for a multi–server network in outpatient pre–operative care. *Production and Operations Management* 27(3):458–479.

Wang, D., K. Muthuraman, D. Morrice. 2019a. Coordinated patient appointment scheduling for a multistation healthcare network. *Operations Research* 67(3):599–618.

Wang, G., L. Jun, W.J. Hopp, F.L. Fazzalari, S.F. Bolling. 2019b. Using patient–specific quality information to unlock hidden healthcare capabilities. *Manufacturing & Service Operations Management* 21(3):582–601.

Wang, S., N. Liu, G.Wan. 2019c. Managing appointment–based services in the presence of walk–in customers. *Management Science* 62(2):667–686.

Wang, W–Y., D. Gupta. 2011. Adaptive appointment systems with patient preference. *Manufacturing & Service Operations* Management 13(3):373–389.

Wang, W–Y., D. Gupta. 2014. Nurse absenteeism and staffing strategies for hospital inpatient units. *Manufacturing & Service Operations Management* 16(3):439–454.

Wang, X., Q. Wu, G. Lai, A. Scheller–Wolf. 2019d. Offering discretionary healthcare services with medical consumption. *Production and Operations Management* 28(9):2291–2304.

Webb, E.M., A.F. Mills. 2019. Incentive–compatible prehospital triage in emergency medical services. *Production and Operations Management* 28(9):2221–2241.

White, D.L., C.M. Froehle, K.J. Klassen. 2011. The effect of integrated scheduling and capacity policies on clinical efficiency. *Production and Operations Management* 20(3):442–455.

White, D.L., E. Torabi, C.M. Froehle. 2017. Ice–breaker vs. standalone: Comparing alternative workflow modes of mid–level care providers. *Production and Operations Management* 26(11):2089–2106.

World Health Organization. 2017. Available at: https://www.who.int/news–room/fact–sheets/detail/human–rights–and–health.

Xiao, W., Y. Xu. 2012. The impact of royalty contract revision in a multistage strategic R&D alliance. *Management Science* 58(12):2251–2271.

Xu, K., C.W. Chan. 2016. Using future information to reduce waiting times in the emergency department via diversion. *Manufacturing & Service Operations Management* 18(3):314–331.

Yamin, D., A. Gavious. 2013. Incentives' effect in influenza vaccination policy. *Management Science* 59(12):2667–2686.

Yan, L. 2017. Good intentions, bad outcomes: The effects of mismatches between social support and health outcomes in an online weight loss community. *Production and Operations Management* 27(1):9–27.

Yang, Y., J.D. Goldhaber–Fiebert, L.M. Wein. 2013. Analyzing screening policies for childhood obesity. *Management Science* 59(4):782–795.

Yankovic, N., L.V. Green. 2011. Identifying good nursing levels: A queuing approach. *Operations Research* 59(4):942–955.

Yom–Tov, G.B., A. Mandelbaum. 2014. Erlang–R: A time–varying queue with reentrant customers, in support of healthcare staffing. *Manufacturing & Service Operations Management* 16(2):283–299.

Zacharias, C., M. Armony. 2017. Joint panel sizing and appointment scheduling in outpatient care. *Management Science* 63(11):3978–3997.

Zacharias, C., M. Pinedo. 2014. Appointment scheduling with no–shows and overbooking. Production and *Operations Management* 23(5):788–801.

Zepeda, E.D., K.K. Sinha. 2015. Towards an effective design of behavioral health care delivery: An empirical analysis of care for depression. *Production and Operations Management* 25(5):952–967.

Zhang, D.J., I. Gurvich, J.A. Van Mieghem, E. Park, R.S. Young, M.V. Williams. 2016. Hospital readmissions reduction program: An economic and operational analysis. *Management Science* 62(11):3351–3371.

Zhang, H., G.S. Zaric, T. Huang. 2011. Optimal design of a pharmaceutical price–volume agreement under asymmetric information about expected market size. *Production and Operations Management* 20(3):334–346.

Zhang, J., B.T. Denton, H. Balasubramanian, N.D. Shah, B.A. Inmans. 2012a. Optimization of prostate biopsy referral decisions. *Manufacturing & Service Operations Management* 14(4):529–547.

Zhang, Y., M.L. Puterman, M. Nelson, D. Atkins. 2012b. A simulation optimization approach to long–term care capacity planning. *Operations Research* 60(2):249–261.

Zhao, H., C. Xiong, S. Gavirneni, A. Fein. 2012. Fee–for–service contracts in pharmaceutical distribution supply chains: Design, analysis, and management. *Manufacturing & Service Operations Management* 14(4):685–699.

Zhou, D., L.C. Leung, W.P. Pierskalla. 2011. Inventory management of platelets in hospitals: Optimal inventory policy for perishable products with regular and optional expedited replenishments. *Manufacturing & Service Operations Management* 13(4):420–438.

Zychlinski, N., A. Mandelbaum, P Momčilović, I. Cohen. 2019. Bed blocking in hospitals due to scarce capacity in geriatric institution – cost minimization via fluid model. *Manufacturing & Service Operations Management* 22(2):396–411.

Chapter 4

Pharmaceutical–CRO Relationships: Are Strategic Partnerships the Way Forward?

4.1 Introduction

Drug discovery and development is a lengthy and costly process which, on average, takes 10 to 15 years and costs $2.6 billion (PhRMA 2016) per drug, with the majority of R&D costs resulting from clinical trials (DiMasi et al. 2016, Drakeman et al. 2022). The importance of launching new drugs to the market quickly, exacerbated by climbing R&D costs, has prompted pharma companies to strive to conduct clinical development in a more time– and cost–efficient manner. Initially providing spillover capacity for pharma, over the last few decades, contract research organizations (CROs) have grown into a multi–billion dollar industry and now execute the lion's share of clinical trials (KPMG 2012).

The relationship between pharma and CROs continues to evolve, with pharma companies increasingly shifting their relationship models from arm's length transactions to preferred providers[1] and multi–year strategic partnerships. Recently, there has been noticeable advocacy for partnerships in the pharma industry, with many industry participants showing an interest in establishing strategic partnerships with CROs (Nice Insight Preclinical and Clinical Contract Research Survey 2017) and holding the belief that partnerships can offer many advantages like accelerating timelines and improving efficiency (Eid 2020). Despite these discussions, it remains unclear when partnerships should be preferred over transactional interactions. According to a recent survey, 25% of outsourced projects are contracted to transactional service providers, 50% are conducted within preferred provider relationships, and the rest are managed through strategic

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[1] Preferred providers are "carefully selected providers that have been thoroughly evaluated through due diligence" (Walker 2015). These relationships are mostly transactional.

partnerships (Nice Insight Preclinical and Clinical Contract Research Survey 2017, Challener et al. 2017). We investigate these strategic partnerships and transactional arrangements with two goals in mind: first, to develop a better understanding of the benefits of each relationship, and second, to examine how pharma managers' choice of outsourcing relationship type can affect development timelines.

In essence, in a strategic partnership, CROs are treated as partners working to achieve common goals rather than simply acting as service providers. A consensus is emerging on the operationalization of strategic partnerships. Industry reports (Schultz 2013, Hughes and Price 2016, Challener et al. 2017) and the academic literature (Azoulay et al. 2010) characterize strategic partnerships through pharma companies' commitment of future business to CROs. This lies in contrast to ad–hoc transactional arrangements for which CROs are hired on a project–by–project or function–by–function basis. In a nutshell, under a strategic partnership, a pharma company commits to a CRO for a longer horizon instead of engaging in one–off transactional interactions.

Commitment can have substantial benefits. First, it implies visibility into the plans and the development pipeline of the pharma company. Ensuring that the CRO has a line of sight facilitates better capacity and resource management, marking a shift from responsive to proactive planning. "*When CROs are given insight into the plans of their strategic partners, they are able to reduce start–up time, staff individual study teams with an optimal mix of expertise and experience, decide for when and where to increase staff, and plan for when and where to invest in new assets and capabilities*" (Hughes and Price 2016). Thus, commitment grants CROs flexibility in allocating adequate and appropriate resources to the pharma company's projects.

Moreover, when CROs are allocated future work and are engaged with planning early on, they can make use of their geographical and regulatory knowledge to provide recommendations and help shape strategy for the trial planning and design (Prior 2015). An example is provided by the relationship between Covance and AstraZeneca (AZ). According to an AZ clinical professional, the partners engage in "*capacity and demand meetings where AZ's and Covance's resourcing managers meet to discuss the AZ portfolio and clinical development plans to allow Covance to select partnership program managers and sites to best fit the requirements of future AZ studies on*

a long–term basis" (Nadarajah 2017). There may also be an element of feedback, learning and continuous development across trials, which to a certain extent is lost in transactional arrangements (Hughes and Price 2016). Lastly, committing to future plans can allow parties to have more time to plan and discuss how they will address circumstances that may inflate timelines and prepare management protocols in advance of trial launch dates.[2]

These advantages of commitment offer the potential to decrease trial duration. In fact, an underlying rationale for strategic partnerships is to speed up development timelines. Since drugs are patented prior to the commencement of clinical trials, delays in development, and subsequently market launches, can be incredibly costly as they erode market exclusivity. For each day a trial is delayed, the cost to the pharma company can range between $600,000 and $8 million (Hargreaves 2016). Delays can even result in a company losing its first–to–market position for a drug candidate (Mclaren 2021). Aside from these significant financial burdens, holdups in market launches mean that drugs are not reaching patients. It has been suggested that strategic partnerships can accelerate speed–to–market by months compared to transactional outsourcing (Schultz 2013)[3].

Common CRO services include drug protocol development, site and investigator selection, patient recruitment, data collection and management, monitoring, and biostatistical analysis (Haeussler and Rake 2017). Typically, the CRO assigns a team to the pharma company's project, and team members works and correspond with scientists from the pharma company. The CRO team usually comprises project managers, clinical research associates, scientists, data managers, and clinical trial associates. A highly capable team with a "mix of academic excellence and strong industry experience, with veteran drug developers and professional managers" can work to achieve the best results for the project and ensure that the "goals of the program are met, to time and budget" (Evotec 2022). For instance, a team with expert knowledge in the therapeutic area for the program under study can assist the pharma company with the trial design, monitoring and data management

[2] It is worth mentioning that CROs stand to benefit from commitment since it offers stability in CRO revenues: "predictability is everything. With transactional arrangements, there is a reliance on predictive models for business since you never know what's coming" (Personal Communication 2020).

[3] The 2015 Vantage Partners survey showed that of those clinical trial sponsors that indicated that outsourced studies are faster [slower] than those conducted in-house, 67% [42%] reported a high degree of [limited] visibility to CROs.

(Ledesma 2020)[4]. On the other hand, team underperformance and mistakes can be very costly for the pharma company. For example, since CRO trial managers are responsible for the recruitment of qualified clinical investigators and sites, the manager's skills, and ability to make good recruitment decisions will influence whether a clinical trial will be completed on time (Credevo 2021). It is thus not surprising that an experienced and talented staff has been listed as the most important factor in CRO selection (Economist Intelligence Unit 2012).

Yet, the increased demand for new talent coupled with the changing technical and scientific requirements (due to the advancement of technologies and the growing level of complexity of therapeutics) has brought to light a pronounced talent scarcity challenge (Sykes 2021, Cini 2022). CROs are not exempt from this challenge and additionally struggle with staff retention problems (with turnover levels exceeding 20% in some years (Fassbender 2019)). As highly capable staff is a key asset but also a scarce resource for CROs, having the team with the *right* skill set (the so–called "A" team) on the job becomes critical for pharma companies. Reminiscent of sourcing flexibility in the supply chain literature, transactional arrangements offer pharma companies the advantage of rehiring only those CROs that have demonstrated high–caliber capability. In contrast, commitment can pose a risk in which CROs may deploy less capable teams once they have been allocated future work by pharma companies.[5] Thus, the problem of CRO "complacency" emerges when CROs attain "partner" status.[6] Clearly, any pharma company's considerations regarding the type of relationship to pursue with a CRO are nontrivial.

To further understand the main tensions in pharma–CRO relationships, we conducted a number of informal interviews with pharma and CRO professionals. These interviews revealed several

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[4] For pharma companies, CRO staff are of crucial importance as CROs assume the role of consulting firms, especially for late phase studies (See Mahan (2014) for a description of clinical trial phases). According to Christopher Gallen, CEO of SK Biopharmaceuticals, the key CRO attribute in successful trial execution is the specific team of people in charge of executing a sponsor's trial. He states: "the reality is that CRO excellence does not vary as much at the company level as it does at the individual project team level" (Wright 2014).

[5] This "bait and switch" tactic is common and cannot be resolved by formal contracts as "buyers (or a court of law) could not distinguish voluntary turnover from opportunistic reassignment to another client" (Azoulay et al. 2010).

[6] Recent operations management (OM) experimental studies have shown that long-term relationships have potential benefits such as improving supply chain efficiency (Davis and Hyndman 2018) but may create incentives for opportunistic behavior (Hyndman and Honhon 2020).

tradeoffs, which serve as the basis for our problem formulation. We set up a three–stage game between a pharma company and a CRO.

With a parameter–rich model, we study how different parameters influence interactions and the benefits of strategic partnerships and transactional arrangements in different settings. In the first stage, the pharma company decides whether to commit to a strategic partnership or form a transactional arrangement with the CRO. Then, in the second stage, the CRO determines whether to deploy the "A" or the "B" team. Lastly, the pharma company decides on whether to maintain the relationship with the CRO. In the case of a strategic partnership, this implies continuation, while in the case of a transactional arrangement, it implies rehiring for the second project. We differentiate between pharma companies with high market potential projects (i.e., the company stands to lose a great deal from trial delays) and those with low market potential. We examine how transparency regarding the market potential of the pharma company's projects influences CRO behavior and, ultimately, the duration of the trial.

Prior work has documented a lack of clarity as to what constitutes a strategic partnership, and this often leads to gaps between what the partnership promises and what it actually delivers (Azoulay et al. 2010). Our analysis allows us to shed light on the *when* and *how* of strategic partnerships by characterizing the conditions under which a pharma company should pursue a strategic partnership with a CRO rather than engage in a transactional arrangement and detailing how the relationship will unfold. Our results demonstrate why transactional arrangements might fail to create value in a wide range of environments and when strategic partnerships can overcome those hurdles. However, we show that despite a strong industry interest in strategic partnerships, one size does not fit all. Although more environments are conducive to strategic partnerships than otherwise (especially for pharma companies with strong pipelines), well–defined projects may be promptly accomplished through one–off interactions. We delineate *when* this will be the case.

In considering the direct and indirect benefits of strategic partnerships and the conditions under which they are realized, we also address the *how* of strategic partnerships: we offer suggestions for reevaluating current industry practices to enhance relationships. For instance, several industry reports and our discussions reveal that a considerable concern for CROs is the lack of transparency

regarding the pharma company's pipeline potential. From the CRO's perspective, this transparency is often seen as necessary for controlling its operations. Yet, our results show that while transparency makes a difference in some instances, strategic partnerships can effectively reduce trial duration even without transparency. Transparency only has value in certain environments in which the CRO's actions differ depending on the pharma company's pipeline potential. We show that these environments are determined by the pharma company's ease of terminating the relationship and the contractual levers that control duration (such as penalties on delays incurred by the CRO).

4.2 Literature Review

Our research closely relates to the OM work in project management. On a broad level, this line of research explores incentives and contracting between an outsourcer and contractor(s) and examines how clients can use various levers to influence contractors' efforts in reducing completion times. Bayiz and Corbett (2005) look at incentive contracts in parallel and serial tasks and derive the first–best, optimal fixed–price and linear incentive contracts and conclude that incentive contracts are always at least (weakly) superior to fixed–price contracts in reducing expected project duration. Chen et al. (2015) examine incentive contracts for serial projects that maximize a client's expected profit and in which contractors determine their work rates taking into account the contract terms; they show that a nonlinear incentive payment contract dominates a fixed–price contract both in terms of profit and schedule. Kwon et al. (2010b) consider channel coordination across contracts in project supply chains by examining nonlinear contracts and demonstrate that time–based and cost–sharing contracts can coordinate the project, while Chen and Lee (2017) show that channel coordination can be achieved via a delivery schedule–based contract. Kwon et al. (2010a) study the impact of contracts with delayed payments on suppliers' effort levels and find that there are cases where the project owner is better off offering a delayed payment regime relative to non–delayed payment. Vairaktarakis (2013) analyze manufacturers' subcontracting strategies so as to minimize their overall completion time and study the competition across manufacturers for the use of third party (service provider) capacity. Rahmani et al. (2017) study how contracts can be used to reduce project duration in a multi–state and multi–period

setting. Dawande et al. (2019) derive optimal contracts between a principal and multiple agents for parallel and sequential projects, and the simplicity of their contracts illustrates that complex contracts are not necessary for maximizing contracts. Our work also relates to Song et al. (2021), who study incentive issues and gaming in risk–sharing partnerships for collaborative projects. According to the authors, in partnerships, in contrast to subcontracting, "a partner may be responsible for other's actions, because its interest is tied to the project."

We contribute to the project management literature in two ways. First, we extend the context to clinical development outsourcing and study project management in pharma–CRO relationships. Second, we evaluate the role of commitment and transparency in this setting to identify the types of environments that necessitate different outsourcing arrangements. We further provide insights on how best to govern each relationship type. In addition, we show that although the recent content in trade publications indicates a growing interest in partnerships, transactional arrangements continue to play a role in clinical trial outsourcing.

Outsourcing relationships in clinical development have typically taken the form of time and materials (T&M) contracts or fixed–price contracts. T&M contracts do not provide financial incentives to decrease the cost or duration of trials. While fixed–price contracts do incentivize CROs to complete trials more efficiently, they lack the flexibility to account for emergent necessary changes to the study (Elvidge 2015); this feature points to the unsuitability of these contracts for long and complex projects such as clinical trials, which necessitate close interaction between the client and provider (Roels 2014). Performance–based contracting (PBC), widely employed in other service outsourcing industries such as information technology and maintenance, repair and operations to manage buyer–supplier relationships, also offers the potential to speed up development timelines. Although penalties for delays in reaching milestones have started to appear in contracts, PBC is not common in the field (Hatcher and Hughes 2016). By examining a simple PBC to govern pharma–CRO relationships, we embark on studying the effectiveness of PBC in the industry and assess whether such contracts can affect clinical trial duration. In doing so, our research also adds to the growing OM literature on PBC in healthcare (Zhang et al. 2016, Andritsos and Tang 2018, Adida and Bravo 2019, Jiang et al. 2012), which has previously focused on healthcare delivery.

Clinical trials constitute a topic of growing interest in the OM literature. Our study broadly relates to the line of research that aims to improve the efficiency of trials through clinical trial design. Several recent and relevant studies explore optimal patient recruitment to address delays to trial timelines (Kouvelis et al. 2017, Tian et al. 2022), utilization of surrogate outcomes to improve clinical trial design–making and speed up trials (Anderer et al. 2021), and flexible trial approval policies that account for trial duration and likelihood of completion (Bravo et al. 2022). Rather than focusing on trial design, we explore how clinical trial duration can be reduced through pharma–CRO relationships. Lastly, researchers have extensively studied R&D alliances between biotechnology and pharma companies (Savva and Scholtes 2014, Bhattacharya et al. 2015, Crama et al. 2017, Tian et al. 2021, Xiao and Xu 2012, Taneri and De Meyer 2017). However, to the best of our knowledge, the relationships between CROs and pharma have not yet been explored. These relationships are fundamentally different from biotech–pharma relationships, which take the form of "innovator/marketer" arrangements.

4.3 Model

A pharma company (P) has two projects[7] $i \in 1,2$ that should be serially completed. It plans to outsource these projects to a CRO (C), and it can do so either by establishing a strategic partnership with the CRO and committing to the CRO for both projects ahead of time or through one–off transactional arrangements for each project. To examine when a strategic partnership is preferred over a transactional arrangement, we model the problem as a three–stage game between the pharma company and the CRO. In stage 1, the pharma company decides whether to commit to the CRO (i.e., strategic partnership) or not (i.e., transactional relationship). In stage 2, the CRO makes its team deployment decision. The pharma company then decides to maintain or terminate the relationship in stage 3. Below, we detail our model and assumptions. Instead of evaluating the optimal contracts, we take the pharma company's perspective and explore the conditions under which it will pursue different relationships. A summary of all the parameters is provided in Table 4.1.

[7] Consistent with practice, the pharma company plans to outsource only a subset of its portfolio to the CRO. We focus on this subset. The remainder of projects will either be kept in-house for strategic reasons and/or contracted out to other service providers with different sets of capabilities.

Table 4.1 Summary of Parameters

P	Pharmaceutical company
C	CRO
i	Indicator for project, $i \in \{1,2\}$
j	Indicator for pharmaceutical company type, $j \in \{S,W\}$
τ	Maximum project duration
s_g	Effect of CRO skills/capability on duration reduction, where $g \in \{A,B\}$ and $s_A > s_B$
w	Effect of commitment for future *work* on duration reduction
F	Fixed payment
f	Fine
m_j	Maximum revenue potential of pharmaceutical company's project, where $m_S > m_W$
b, $1-b$	CRO beliefs regarding m_j, where $0 \leq b \leq 1$
l	Loss in revenue, where $0 < l \leq 1$
e	Exit fee, where $e > 0$
d_o	Duration of outside option, where $0 \leq d_o \leq \tau$
d_i	Duration of project i, where $d_i \geq 0$
T_i	Total transfer payment to CRO for project i, where $T_i \geq 0$
K_g	CRO cost of deploying either group: "A" or "B" team where $K_A = k^2 \geq 0$ and $K_B = 0$
$R_{i,j}$	Pharmaceutical company revenue for project i and type j, where $R_{i,j} \geq 0$
Π_i^C	CRO payoff for project i
$\Pi_{i,j}^P$	Pharmaceutical company payoff for project i and type j
c	Pharmaceutical company commitment, $c \in \{0,1\}$
h	Honoring of commitment, $h \in \{0,1\}$
r	Rehiring of CRO, $r \in \{0,1\}$

Pharmaceutical company's portfolio strength: Pharma companies differ with respect to the strength of their portfolios. We differentiate between companies with portfolios composed of weak projects and those composed of strong ones. A pharma company with "strong" projects stands to earn large revenues and consequently to suffer large losses from trial delays. On the other hand, a company with "weak" projects expects lower earnings from its projects and losses resulting from delays are smaller in magnitude. We let m_j represent the maximum revenue potential for the pharma company's project, where $j \in W, S$. Let W stand for weak, S stand for strong and $m_w < m_S$. The value of m_j is private information for the pharma, although, the CRO has beliefs regarding m_j. Let b represent the CRO's belief that the pharma company's portfolio is strong and $1-b$ be the CRO's belief that the portfolio is weak. Although much information regarding a pharma company's endeavors may be publicly available, it is reasonable to assume that the importance and potential of projects in its pipeline is private information for the company. In other words, a CRO faces uncertainty regarding the strength of the pharma company's portfolio.

Project duration: As is common in the project management literature (e.g., Song et al. (2021)), we follow Bayiz and Corbett (2005) and assume each project has a duration d_i in which some maximum duration τ can be reduced by the actions of actors:

$$d_i(s_g, c) = \tau - s_g - wc$$

for $i \in 1,2$ and $g \in A, B$ and $s_A > s_B$. Both projects have the same maximum duration. Duration reduction can be achieved both by the CRO's team deployment decision (s_g relates to the skill level of each group, where $g = A$ ($g = B$) represents the reduction in duration as a result of the CRO allocating its "A" ("B") team to the project, respectively) and by the pharma company's commitment decision (where $c \in 0,1$). The term wc represents the reduction in duration stemming from the allocation of future work.

The CRO's payoff: The CRO receives a transfer payment from the pharma company for each project, $T_i(d_i) = F - fd_i$ for $i \in 1,2$. The payment for each project consists of a fixed payment, F, and a linear incentive term dependent on project duration (in this case, a penalty or a fine, f). We assume that the fixed payment and fines are the same across projects. The CRO incurs a cost, K_g, for deploying its "A" or "B" team to a project. We normalize K_B to zero and let $K_A = k^2$, where k is a constant. The CRO's payoff for each project when team g is deployed is

$$\Pi_i^C = T_i(d_i) - K_g = F - fd_i - K_g$$

The CRO is paid upon completion of each project and maximizes its payoff.

The pharmaceutical company's payoff: The pharma company receives a revenue, $R_{i,j}(d_i) = m_j(1 - ld_i)$, for each project, which is decreasing in d_i. The maximum revenue potential, m_j, depends on the pharma company's type. Faster project completion times result in a quicker time to market and a longer revenue generation period under patent protection. The value of the loss, l, can be very large, as pharma companies can lose up to $8 million each day a trial is delayed

(Hargreaves 2016). The pharma company's payoff for each project is the revenue it earns less the payment made to the CRO:

$$\Pi_{i,j}^{P} = R_{i,j}(d_i) - T_i(d_i) = m_j(1 - ld_i) - (F - d_i)$$
$$= (m_j - F) - (m_j l - f)d_i \quad (1)$$

The pharma company aims to maximize its total profits.

Timeline of events: The sequence of events is outlined in Figure 4.1.

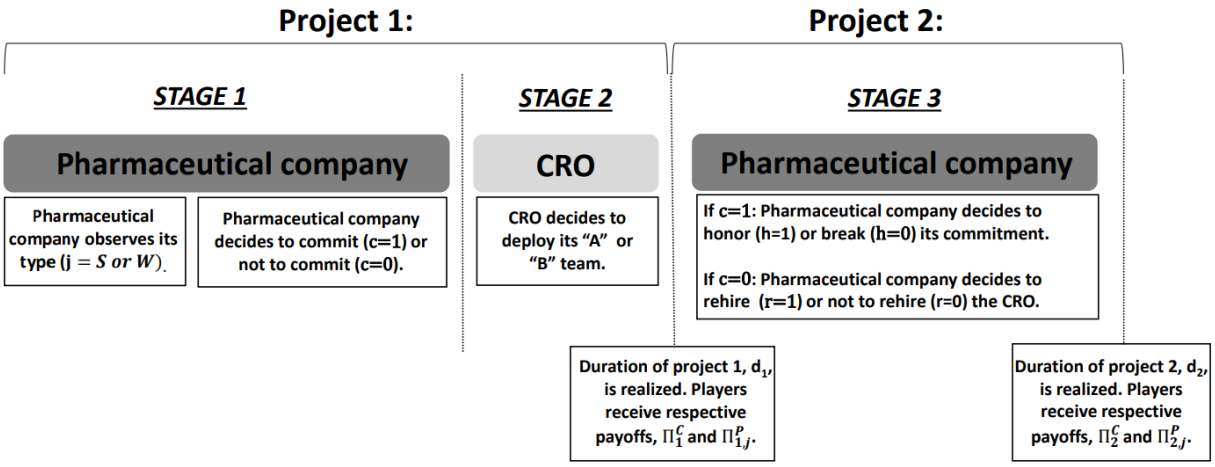

Figure 4.1 Sequence of events in the partnership. The duration of project 1 (project 2) is realized in period 1 (period 2). Therefore, we use project *i* and period *i* interchangeably in the rest of the paper.

In stage 1, the pharma company observes its type (S or W) and chooses whether to commit to the CRO ($c = 1$) or not ($c = 0$). In either case, the CRO then chooses whether to allocate an "A" team or a "B" team to execute project 1 in stage 2. At the end of stage 2, the duration of project 1, d_1, is realized. The CRO is paid for project 1 and both parties receive their respective payoffs, Π_1^C and $\Pi_{1,j}^P$. If the pharma company does not commit to the CRO ($c = 0$) in stage 1, the CRO is unaware of project 2. Having observed the duration of project 1, the pharma company decides whether to rehire the same CRO team ($r = 1$) to execute project 2 in stage 3. If the pharma company decides not to rehire the CRO ($r = 0$), the pharma company assigns project 2 to another CRO (i.e., pursues its outside option). In this case, we assume the duration of project 2 is d_o, the

average industry duration. We also note that no commitment was made to the CRO and therefore if the pharma company chooses not to rehire the CRO for the second project, it does not need to pay the CRO an exit fee. At the end of stage 3, the pharma company earns $\Pi_{2,j}^{P}(d_o) = m_j(1 - ld_o) - (F - fd_o)$. If, instead, the CRO is rehired for project 2 ($r = 1$), the CRO executes project 2. At the end of stage 3, the duration of project 2, d_2, is realized and both players receive their respective payoffs, Π_2^C and $\Pi_{2,j}^{P}$.

On the other hand, if the pharma company commits to the CRO ($c = 1$) in stage 1, the CRO is aware of project 2, which will commence after the completion of project 1. After the execution of project 1, d_1 is realized and the pharma company decides whether to honor ($h = 1$) or break ($h = 0$) its commitment to the CRO regarding project 2. If the pharma company breaks its commitment ($h = 0$), the CRO is paid an exit fee, e, which is intended to compensate for the CRO's lost flexibility in redeploying its resources as well as lost revenues.[8] The pharma company assigns project 2 to its outside option and earns $\Pi_{2,j}^{P}(d_o) = m_j(1 - ld_o) - (F - fd_o) - e$. If the pharma company honors its commitment ($h = 1$), the CRO executes the project in period 2. At the end of period 2, the duration of project 2, d_2, is realized and the CRO is paid. Players receive their respective payoffs, Π_2^C and $\Pi_{2,j}^{P}$.

From Equation (1), we observe that when $m_j l < f$, the pharma company prefers a less capable option (i.e., one which results in a longer duration). This is because although the pharma company will earn more revenue with a more capable option, the company will also have to make larger payments to the more capable vendor (since as duration decreases, the vendor is charged less in fines). Thus, when the pharma company faces a small revenue loss compared to the fine, the gain in revenue does not justify these higher payments. Typically, however, pharma companies make very large revenues and therefore stand to suffer large losses on their products in comparison to their outsourcing expenses. In such a case, the pharma company would like to minimize duration and pursue the most capable outsourcing option since the revenue gains from a shorter duration

[8] Resource and capacity redeployment is complicated by customer concentration, an outcome of strategic partnerships; for example, only five clients account for 50% of Parexel's service revenue (Results Healthcare 2013). Due to the dependency on a small number of clients, project cancellations can cause a CRO difficulty in redeploying its staff (Results Healthcare 2013).

offset higher payments made to the CRO due to a reduction in fines. Therefore, going forward, we focus our attention on the situation where $m_j l > f$, which is closer to reality.

4.4 Full Information Case

In this section, we present the results of the full information model in which the CRO knows the strength of the pharma company's portfolio with certainty. That is, the CRO has transparency of the pharma company's portfolio and knows whether it has entered into a transactional/strategic relationship with a pharma company that has a weak portfolio or a strong portfolio. Using backwards induction, we solve for the subgame perfect Nash equilibria (SPNE) of the three–stage sequential game (Figure 4.1) and discuss the outcomes of each stage.

4.4.1 Stage 3: Maintain or Terminate Relationship with the CRO?

We first characterize the pharma company's best response after the completion of project 1: in this stage, the company decides whether to rehire/honor the commitment to the team for the second project.

> LEMMA 1 **(More capable outsourcing option is preferred).** *When $mj\ l > f$ and not factoring in the exit fee, the pharmaceutical company prefers the more capable outsourcing option (resulting in a shorter duration).*

Proof: All proofs are in the Appendix.

Following naturally from Lemma 1, Corollary 1 summarizes the pharma company's third–stage decision when the CRO chooses to deploy its "A" team.

> COROLLARY 1 **(Maintain the relationship with the "A" team).** *When the CRO deploys its "A" team, the pharmaceutical company's best response is to maintain the relationship.*

By Corollary 1, if the CRO deploys its most capable team to work on the pharma company's projects, the company prefers to maintain rather than terminate the relationship for the second project. However, if the CRO deploys its "B" team, the pharma company must decide whether to maintain the relationship with the "B" team for project 2 or pursue its outside option. Proposition 1 summarizes the pharma company's rehiring decision. Let $\delta = d(s_B, 1) - d_o$ [9] be the difference between the duration achieved with a "B" team and the outside option duration.

> PROPOSITION 1 **(Maintain the relationship with the "B" team).** *When the CRO deploys its "B" team, the pharmaceutical company's best response is to*
> *(a) maintain the relationship with the "B" team if either* $d_o > d(s_B, c)$ *or if* $d_o < d(s_B, c)$ *and* $ec > \phi_j \delta$*; and*
> *(b) pursue its outside option if* $d_o < d(s_B, c)$ *and* $ec < \phi_j \delta$.

The decision whether to maintain a relationship with the CRO's "B" team depends on the team's capability and the outside option. When $d_o > d(s_B, c)$, since the pharma company is interested in pursuing the most capable option (Lemma 1), it will maintain the relationship with the more capable "B" team. On the other hand, when $d_o < d(s_B, c)$, the outside option results in a shorter duration than relying on the "B" team. The "B" team will not be rehired under a transactional relationship. Although the pharma company would similarly like to break its commitment in a strategic partnership, the decision also depends on the exit fee, e. The pharma company expects to earn more revenue with the outside option than with the "B" team ($R_{2,j}(d_o) > R_{2,j}(d_2(s_B, 1))$). However, since a shorter duration means that lower fines are charged, the pharma company must make a higher payment to the outside option ($T_2(d_o) > T_2(d_2(s_B, 1))$). We let $\phi_j = m_j\, l - f$ be the pharma company's gain in revenue, less the loss in fines, earned from a reduction in duration, i.e., ϕ_j is the pharma's net benefit from pursing a more capable outsourcing option. That is, $\phi_W \delta$ and $\phi_S \delta$ represent the gain that a pharma company with a weak/strong project portfolio earns, respectively, by pursing the outside option.

[9] For the sake of simplicity, going forward, we omit the project indicator *i* from duration.

If $e < \phi_W \delta$, the exit fee is low, meaning that the pharma company can afford to break its commitment to the "B" team, pay the exit fee and still gain from pursuing its outside option. As the exit fee increases, the company may find it prohibitive to break its commitment. If $\phi_W \delta < e < \phi_S \delta$, only a pharma company with a strong project portfolio can break its commitment to the CRO. If $e > \phi_S \delta$, under a very high exit fee, the pharma company finds it prohibitive to terminate the relationship regardless of its portfolio strength, i.e., the gain in payoffs from pursuing the more capable outside option does not offset the high exit fee. Figure 4.2 summarizes these results and displays the outcomes of the third stage for "B" team deployment in a strategic partnership.

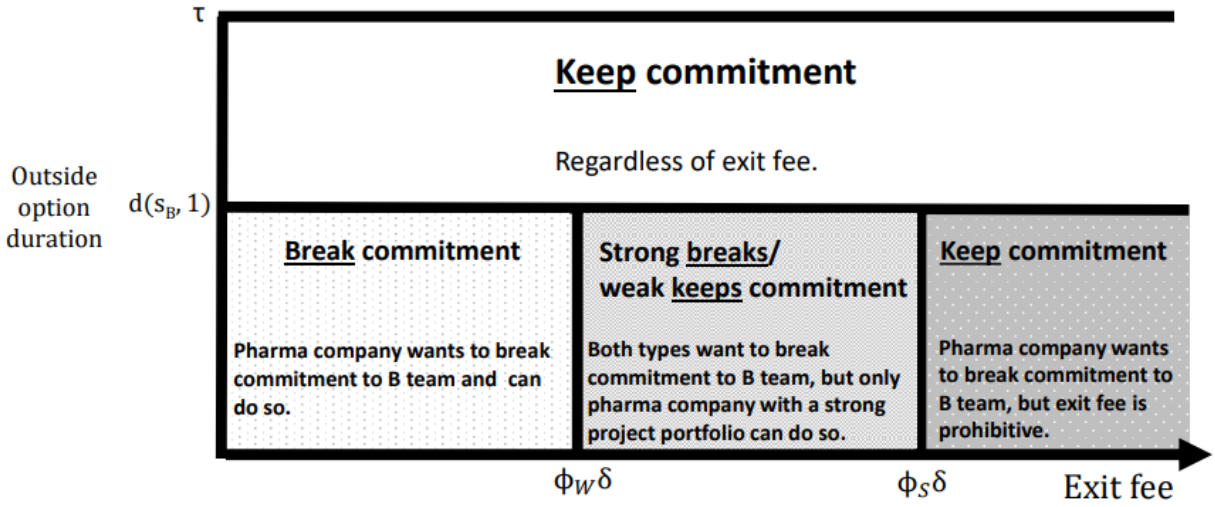

Figure 4.2 Stage 3 outcomes for "B" team in a strategic partnership.

4.4.2 Stage 2: CRO's Team Deployment Decision – "A" Team or "B" Team?

Having solved for the pharma company's best response in the third stage, we next examine the CRO's decision regarding the deployment of its "A" or "B" team in the second stage. A comparison of the payoffs shows that the main drivers of the CRO's decision to deploy an "A" or a "B" team are the fine and fixed payment. Let $\alpha = f(s_A - s_B)$ represent the benefit to the CRO from a reduction in fines through deploying an "A" team versus a "B" team. We refer to a low fine environment as one where the benefit is less than the cost of deploying an "A" team (i.e., $\alpha < K_A$), and a high fine environment as one in which the fine reduction achieved with an "A" versus a "B" team is larger than the cost of an "A" team (i.e., $\alpha > K_A$).

PROPOSITION 2 **(Deploy "A" or "B" team?).** *The CRO deployment decision is as follows:*

(i) If the pharmaceutical company's best response is to maintain the relationship following "B" team deployment (Proposition 1(a)), then if $\alpha \underset{[<]}{>} K_A$ *(i.e., high [low] fine environment), the CRO will deploy an "A" ["B"] team.*

(ii) If the pharmaceutical company's best response is to pursue its outside option following "B" team deployment (Proposition 1(b)), then if $F + \alpha - 2K_A \underset{[<]}{>} fd(s_A, c) + ec$ *(i.e., high [low] fixed payments or low [high] exit fee), the CRO will deploy an "A"["B"] team.*

In transactional arrangements ($c = 0$), the CRO's decision depends on whether the transactional arrangement will be maintained or terminated. When the pharma company does not rehire the "B" team, the CRO's decision depends on the fixed payment (Proposition 2(ii)). That is, if the fixed payment is high, the CRO will deploy its "A" team, and if it is low, the CRO will deploy its "B" team. If, on the other hand, the pharma company rehires the "B" team, the CRO's decision depends on the fine environment (Proposition 2(i)) and subsequently on the fine (f), the marginal effectiveness of the "A" team in reducing duration ($s_A - s_B$), and the cost of the "A" team (K_A). In a high fine environment, the CRO deploys its "A" team while in a low fine environment, the CRO prefers to deploy its "B" team.

These results show that as the fine (f) decreases, marginal effectiveness of the "A" team ($s_A - s_B$) decreases, or the cost of an "A" team (K_A) increases, it becomes less likely that a CRO deploys its "A" team. That is, the current processes in place (a reliance on reverse auctions and a prevalence of T&M and fixed–price contracts) or particular cost environments may render transactional relationships ineffective. Therefore, our results may offer one explanation as to why, in practice, more and more pharma companies are moving away from transactional arrangements to multi–year agreements with CROs.

Our analysis shows that in a transactional relationship two levers can govern the relationship: the fixed payment and the fine. When there is no prospect of a pharma company rehiring the "B" team,

a high fixed payment serves as a "carrot" motivating the CRO to instead deploy its "A" team and get the most value out of a transactional relationship. This directly contrasts with the common practice of reverse auctions whereby CROs submit bids to be selected as the pharma company's vendor for a project. This process often results in CRO overcommitment, lowballing and price wars arising from the pressure to win contracts. Procurement based on the lowest price often leads to change orders and subsequent delays during trial execution. Thus, *managers should shake off the notion that "transactional" means "cheap."* In fact, this result lends support to the idea of paying a retainer in order to "ring–fence" top teams.

Alternatively, even when there is the possibility of repeat business for a CRO's "B" team, a high fine acts as a "stick" that puts pressure on the CRO to bring the "A" team forward. *Performance–based contracts can thus play a role in reducing duration,* taking the place of commonly employed T&M and fixed–price contracts.

We find that in strategic partnerships ($c = 1$), the main drivers of the CRO's team deployment decision are the fine and exit fee. Similar to the case of transactional relationships, when the pharma company maintains the relationship with the "B" team ($h = 1$), the CRO's team deployment decision is irrespective of the exit fee and instead depends on the fine (Proposition 2 (i)). The CRO decides between deploying its "A" team twice or its "B" team twice. A high fine environment drives the CRO to deploy its "A" team. On the contrary, in a low fine environment, the benefit the CRO receives through reducing fines by using its "A" team does not justify the cost of the "A" team. When the pharma company pursues its outside option following "B" team deployment ($h = 0$), the CRO's team deployment decision is influenced by the exit fee (Proposition 2(ii)). That is, the CRO deploys its "A" team when the exit fee is low and deploys its "B" team otherwise. This result suggests that pharma companies should be mindful of the fact that if the CRO stands to receive high compensation upon the dissolution of partnership, this may have unintended consequences on CRO actions throughout the relationship.

In practice, the ability to terminate the partnership will depend on the outside options available to the pharma company as well as the exit fee it incurs for dissolving the relationship. Some of our pharma respondents stated that their companies do discontinue contracts with CROs, while others

mentioned that "partnership termination" can take a more subtle form, such as reducing a CRO's workload, not considering them for new work that arises, or reallocating different elements of clinical development (e.g., medical writing, biometrics, clinical operations, study design, etc.) across strategic partners. Even so, several of our pharma interviewees expressed reluctance to terminate existing partnerships, citing the time and difficulty involved in "getting the ball rolling again." This can be considered as a high switching cost of an alternative provider and factored into the outside option duration. Our results indicate that in situations where it may be prohibitive for the pharma company to terminate the relationship following "B" team deployment (either due to a lack of a better outside option or to high exit fees), PBC can serve to govern the partnership. Again, fines can act as a "stick" to motivate the CRO to bring its "A" team instead.

These insights are given in the first two rows of Table 4.2, which summarizes the main results obtained in Sections 4.4 and 4.5.

Table 4.2 Summary of Results

Current practices	... need to be reevaluated.
Underbidding and price wars resulting in procurement based on lowest price.	Large fixed payments need to be made to ensure the "A" team in transactional relationships.
Prevalence of fixed-price and time-and-materials contracts.	There is a place for performance-based contracts in accelerating trial development.
Monitoring and micromanagement in strategic partnerships to ensure CRO performance.	The possibility partnership dissolution motivates good performance without high payments or penalizations.
Ring-fencing CRO "A" teams at high costs.	There is value in strategically partnering with "B" teams.
Overemphasis on a single type of outsourcing relationship.	One size *does not* fit all: commitment may or may not be beneficial.
Disclosure of the pharma company's pipeline necessary for controlling the CRO's operations.	Transparency makes a difference in certain cases, yet strategic partnerships can be effective even without transparency.

4.4.3 Stage 1: Transactional Relationship or Strategic Partnership?

In the first stage, the pharma company faces the decision of whether to pursue a transactional relationship or a strategic partnership with the CRO. To make this decision, it considers the CRO's best response in the second stage, its subsequent decision to maintain or terminate the relationship in the third stage, and ultimately its payoffs. Recall that one of three situations can occur under each relationship: the "A" team executes both projects, the "B" team executes both projects, or the "B" team executes the first project and the outside option executes the second project. This leads to the 25 equilibria characterized in Theorem 1. Below, we discuss the noticeable predominance for strategic partnerships (particularly for pharma companies with strong pipelines), the key drivers in the choice between a strategic partnership and a transactional arrangement, and the environment in which the greatest value can be derived from a strategic partnership.

> THEOREM 1 **(Commit or do not commit?).** *The pharmaceutical company's optimal commitment decision is influenced by the effectiveness of commitment on duration reduction w, the outside option do, and the exit fee e, as characterized in Table 4.3.*

To understand how Table 4.3 works, consider an example, say Equilibrium 16 (Eq. 16). Under Eq. 16, a pharma company with a strong portfolio commits, the CRO deploys its "A" team, and the pharma company maintains the relationship. On the other hand, a pharma company with a weak portfolio does not commit and the CRO deploys its "B" team, which is not subsequently rehired. The rationale behind the backward induction is as follows: since the outside option is good ($d_o < d(s_B, 1) < d(s_B, 0)$), both types of pharma company do not rehire the "B" team under a transactional arrangement (Proposition 1(b)). Since both types pursue the outside option following "B" team deployment and fixed payments are low ($F + \alpha - 2K_A < fd(s_A, 0)$), the CRO deploys its "B" team (Proposition 2(ii)). In a strategic partnership, although both types prefer the outside option to the CRO's "B" team, since the exit fee is moderate ($\phi_W \delta < e < \phi_S \delta$), the strong type terminates the partnership (Proposition 1(b)), but the weak type maintains it (Proposition 1(a)(ii)).

Table 4.3 Stage 1 outcomes

Eq.	Stage 3 (Proposition 1) Exit fee	Best response (SP/TR)	Fine	Stage 2 (Proposition 2) CRO compensation	Best response (SP/TR)	Stage 1 Commit. Gain	Outcome
When the outside option is not viable: $d(s_B,1) < d(s_B,0) < d_o$							
1		Both: Maintain "A"/Rehire "A"	$\alpha > K_A$		"A"/"A"		Both: SP
2		Both: Maintain "B"/Rehire "B"	$\alpha < K_A$		"B"/"B"		Both: SP
When the outside option is bad: $d(s_B,1) < d_o < d(s_B,0)$							
3		Both: Maintain "A"/Rehire "A"	$\alpha > K_A$		"A"/"A"		Both: SP
4		Both: Maintain "B"/Fire "B"	$\alpha < K_A$	$fd(s_A,0) > F + \alpha - 2K_A$	"B"/"B"		Both: SP
5		Both: Maintain "B"/Rehire "A"	$\alpha < K_A$	$fd(s_A,0) < F + \alpha - 2K_A$	"B"/"A"	$w > s_A - s_B$	Both: SP
6		Both: Maintain "B"/Rehire "A"	$\alpha < K_A$	$fd(s_A,0) < F + \alpha - 2K_A$	"B"/"A"	$w < s_A - s_B$	Both: TR
When the outside option is good: $d_o < d(s_B,1) < d(s_B,0)$							
7	$\phi_W\delta < \phi_S\delta < e$	Both: Maintain "A"/Rehire "A"	$\alpha > K_A$		"A"/"A"		Both: SP
8	$\phi_W\delta < \phi_S\delta < e$	Both: Maintain "B"/Fire "B"	$\alpha < K_A$	$fd(s_A,0) > F + \alpha - 2K_A$	"B"/"B"	$w > d_2(s_B,1) - d_o$	Both: SP
9	$\phi_W\delta < \phi_S\delta < e$	Both: Maintain "B"/Fire "B"	$\alpha < K_A$	$fd(s_A,0) > F + \alpha - 2K_A$	"B"/"B"	$w < d_2(s_B,1) - d_o$	Both: TR
10	$\phi_W\delta < \phi_S\delta < e$	Both: Maintain "B"/Rehire "A"	$\alpha < K_A$	$fd(s_A,0) < F + \alpha - 2K_A$	"B"/"A"		Both: TR
11	$\phi_W\delta < e < \phi_S\delta$	Both: Maintain "A"/Rehire "A"	$\alpha > K_A$	$\max\{e + fd(s_A,1), fd(s_A,0)\} < F + \alpha - 2K_A$	"A"/"A"		Both: SP
12	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "A"/Rehire "A" Strong: Terminate "B"/Rehire "A"	$\alpha > K_A$	$fd(s_A,0) < F + \alpha - 2K_A < e + fd(s_A,1)$	"A"/"A" "B"/"A"		Weak: SP Strong: TR
13	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Rehire "A" Strong: Terminate "B"/Rehire "A"	$\alpha < K_A$	$fd(s_A,0) < F + \alpha - 2K_A < e + fd(s_A,1)$	"B"/"A" "B"/"A"		Weak: TR Strong: TR
14	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Rehire "A" Strong: Maintain "A"/Rehire "A"	$\alpha < K_A$	$\max\{e + fd(s_A,1), fd(s_A,0)\} < F + \alpha - 2K_A$	"B"/"A" "A"/"A"		Weak: TR Strong: SP
15	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Fire "B" Strong:Maintain "A"/Fire "B"	$\alpha < K_A$	$e + fd(s_A,1) < F + \alpha - 2K_A < fd(s_A,0)$	"B"/"B" "A"/"B"	$w > d_2(s_B,1) - d_o$	Weak:SP Strong:SP
16	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Fire "B" Strong:Maintain "A"/Fire "B"	$\alpha < K_A$	$e + fd(s_A,1) < F + \alpha - 2K_A < fd(s_A,0)$	"B"/"B" "A"/"B"	$w < d_2(s_B,1) - d_o$	Weak:TR Strong:SP
17	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Fire "B" Strong: Terminate "B"/Fire "B"	$\alpha < K_A$	$\min\{e + fd(s_A,1), fd(s_A,0)\} > F + \alpha - 2K_A$	"B"/"B" "B"/"B"	$w > d_2(s_B,1) - d_o$ $w(m_S l - f) > e$	Weak:SP Strong: SP
18	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Fire "B" Strong: Terminate "B"/Fire "B"	$\alpha < K_A$	$\min\{e + fd(s_A,1), fd(s_A,0)\} > F + \alpha - 2K_A$	"B"/"B" "B"/"B"	$w < d_2(s_B,1) - d_o$ $w(m_S l - f) > e$	Weak:TR Strong: SP
19	$\phi_W\delta < e < \phi_S\delta$	Weak: Maintain "B"/Fire "B" Strong: Terminate "B"/Fire "B"	$\alpha < K_A$	$\min\{e + fd(s_A,1), fd(s_A,0)\} > F + \alpha - 2K_A$	"B"/"B" "B"/"B"	$w < d_2(s_B,1) - d_o$ $w(m_S l - f) < e$	Weak:TR Strong: TR
20	$e < \phi_W\delta < \phi_S\delta$	Both: Maintain "A"/Rehire "A"		$\max\{e + fd(s_A,1), fd(s_A,0)\} < F + \alpha - 2K_A$	"A"/"A"		Both:SP
21	$e < \phi_W\delta < \phi_S\delta$	Both: Terminate "B"/Rehire "A"		$fd(s_A,0) < F + \alpha - 2K_A < e + fd(s_A,1)$	"B"/"A"		Both:TR
22	$e < \phi_W\delta < \phi_S\delta$	Both: Maintain "A"/Fire "B"		$e + fd(s_A,1) < F + \alpha - 2K_A < fd(s_A,0)$	"A"/"B"		Both:SP
23	$e < \phi_W\delta < \phi_S\delta$	Both: Terminate "B"/Fire "B"		$\min\{e + fd(s_A,1), fd(s_A,0)\} > F + \alpha - 2K_A$	"B"/"B"	$w(m_W l - f) > e$	Both:SP
24	$e < \phi_W\delta < \phi_S\delta$	Weak: Terminate "B"/Fire "B" Strong: Terminate "B"/Fire "B"		$\min\{e + fd(s_A,1), fd(s_A,0)\} > F + \alpha - 2K_A$	"B"/"B" "B"/"B"	$w(m_W l - f) < e$ $w(m_S l - f) > e$	Weak:TR Strong: SP
25	$e < \phi_W\delta < \phi_S\delta$	Both: Terminate "B"/Fire "B"		$\min\{e + fd(s_A,1), fd(s_A,0)\} > F + \alpha - 2K_A$	"B"/"B"	$w(m_S l - f) < e$	Both:TR

Since the weak type pharma company maintains the partnership with the "B" team and it is a low fine environment ($\alpha < K_A$), the CRO deploys its "B" team (Proposition 2(i)) for the weak type company. However, in a strategic partnership with the strong type pharma company, since the company terminates the partnership with the "B" team and the exit fee is low ($e + fd(s_A, 1) < F + \alpha - 2K_A < fd(s_A, 0)$), the CRO deploys its "A" team (Proposition 2(ii)).

Given stage 2 and 3 best responses, it is not surprising that the strong type prefers a strategic partnership with the CRO "A" team to working with the "B" team under a transactional arrangement. The weak type faces the CRO's "B" team in both a strategic partnership and a transactional arrangement. A strategic partnership results in a higher payoff from the first project for the weak type due to the gain from commitment (w) but a lower payoff for the second project (due to the opportunity cost of not pursing a more capable outside option). Since $w < d_2(s_B, 1) - do$, the weak type prefers to take a hit on its payoff from the first project in order to greatly reduce the duration of the second project by entering into a transactional arrangement.

4.4.4 Insights from the Full Information Case

Several key insights emerge from analysis of the full information game. In the majority of cases, a strategic partnership is preferred. The strong type prefers a strategic partnership under 17 circumstances and opts for a transactional arrangement under eight[10]. In comparison, the weak type prefers a strategic partnership under 14 circumstances and opts for a transactional arrangement under eleven[11]. This suggests that there are more environments conducive for strategic partnerships than not, especially for pharma companies with strong pipelines. Delving into the reasons why a strategic partnership is preferred, we reveal six additional insights.

First, even if the "A" team is deployed in a transactional arrangement, the pharma company prefers to enter into a strategic partnership with the CRO's "A" team so that it gains from the added benefit of commitment in reducing duration (Eq. 1, 3, 7, 11, 20 for both types, Eq. 12 for the weak type, and Eq. 14 for the strong type). Second and not surprisingly, the pharma company also prefers a

[10] Eq. 6, 9, 10, 12, 13, 19, 21, 25

[11] Eq. 6, 9, 10, 13, 14, 16, 18, 19, 21, 24, 25

strategic partnership with an "A" team if it faces working with the CRO's "B" team under a transactional arrangement (Eq. 22 for both types, and Eq. 15, 16 for the strong type).

The final four insights relate to four circumstances in which a pharma company strategically partners with a "B" team. In the first case, the pharma company commits to a "B" team to avoid having to rely on a poor outside option (Eq. 2, 4). Practically, this could represent various situations such as unfavorable bids, a limited selection of providers due to budget considerations or the specifics of the project, or constraints on provider choice at the company level (e.g., a shortlist of approved CROs). In the second case, we find that the pharma company commits to a less capable "B" team if commitment is more effective in reducing duration than a capable (uncommitted) "A" team, i.e., $w > s_A - s_B$ (Eq. 5). A strategic partnership is thus favorable in cases where CRO flexibility (in resource and capacity planning, reduction in set–up costs, etc.) is crucial to the timely completion of the project. In the final two cases, commitment results in higher payoffs for the first project and lower payoffs for the second project. By committing to a "B" team, the pharma company takes a hit on its payoff for the second project, either through the opportunity cost of not pursing a more capable outside option, i.e., $w > d_2(s_B, 1) - d_o$ (Eq. 8 for both types and Eq. 15, 17 for the weak type) or through having to pay an exit fee, i.e., $w(m_S l - f) > e$ (Eq. 23 for both types and Eq. 17, 18, 24 for the strong type) to greatly reduce the duration of the first project. Importantly, these results show that although employing a CRO's "A" team is desirable, when the gain from commitment is instrumental in reducing duration, pharma companies may be willing to "offer a helping hand" and forge partnerships with less experienced "lower tier" teams. In this way, commitment serves as a substitute for CRO capability. Even though the criticality of the "A" team was widely acknowledged by our interviewees, we show that it is not always the case that working with the "A" team is the only way to reduce clinical trial duration.[12]

Investigating the reason why a pharma company with a strong portfolio may prefer a strategic partnership more often than a pharma company with a weak portfolio necessitates a discussion of

[12] Upon seeing this result, one of our interviewees shared anecdotal support for this theoretical finding and stated that such an action deviated from the norm and was undertaken in response to the disruption caused by the pandemic: "*A team can grow with the study. We worked with a smaller CRO; the team was not the "A" team but was very eager to learn. Through collaboration and two-way communication, we were able to develop an adaptive protocol and execute a challenging cardiovascular drug study during the first waves of the COVID-19 pandemic.*"

the exit fee. We note that the exit fee serves two important purposes in strategic partnerships. First, it determines whether the threat of the pharma company breaking its commitment to the CRO is credible. Depending on the environment, any pharma company, only one with a strong portfolio, or no pharma company may afford to break its commitment to the CRO and pay the exit fee. Second, the exit fee also influences the CRO's decision whether to deploy a "B" team as it represents the compensation it will receive if the partnership is terminated. For these reasons, it becomes clear that *the exit fee is critical to the success of a strategic partnership*.

If the threat of the pharma company breaking its commitment is credible, meaning the exit fee is not prohibitive ($e < \phi_j \delta$), then the exit fee should also be low enough ($e < F + \alpha - 2K_A - fd(s_A, 1)$) to ensure that the CRO does not deploy its "B" team in the hopes that the pharma company will terminate the relationship ($h = 0$) and pay the CRO a hefty compensation. If, on the other hand, the exit fee is so high that it becomes prohibitive ($e > \phi_j \delta$) for the pharma company to break its commitment (i.e., the threat of breaking commitment is not credible), the exit fee no longer explicitly factors into the CRO's team deployment decision. In these instances, penalties can play a role in governing the maintained relationship and high fines ($\alpha > K_A$) become vital in ensuring that the CRO deploys its "A" team. When fines are low, the CRO will not find it worthwhile to reduce duration by deploying its "A" team. Under moderate exit fees ($\phi_W \delta < e < \phi_S \delta$), the weak type pharma company does not have a credible threat of termination in the strategic partnership. In such a case, the strategic partnership can only be governed by high fines. Consequently, in low fine environments the weak type instead opts for a transactional arrangement with the CRO, explaining why a transactional arrangement is pursued more often by pharma companies with weak pipelines.

Several remarks regarding transactional arrangements are in order. At a high level, a transactional arrangement is preferred to a strategic partnership when the *benefits of commitment, as discussed above, are not highly consequential in reducing duration* (i.e., $w < s_A - s_B$, $w < d_2(s_B, 1) - d_o$, or $w(m_S l - f) < e$). In such cases, a transactional arrangement offers the pharma company two means of recourse. First, if the CRO does not anticipate repeat business following "B" team deployment and if fixed payments are high, the CRO deploys its "A" team (Proposition 2(ii)). Thus, the pharma company can still benefit from the deployment of the CRO's top tier team (Eq.

6, 10, 12, 13, 21 for the strong type, and 6, 10, 13, 14, 21 for the weak type). If, however, fixed payments are low, a transactional arrangement allows the pharma company the flexibility to pursue a good outside option for the second project (Eq. 9, 19, 25 for both types and 16, 18, 24 for the weak type). This illustrates that when the benefits of commitment are limited, there is still a place for transactional interactions and parties do not need to enter into long–term strategic partnerships. In fact, this alludes to an argument expressed by some of our interviewees regarding the underlying reason why pharma companies approach CROs: do projects require "brains" or "brawn"? Our results suggest that *strategic partnerships are preferred for complex projects* (such as first–in–class drugs, which uncover new mechanisms of action) that necessitate a high degree of foresight and dialogue (i.e., commitment is highly effective in reducing duration). On the other hand, *well–defined projects (such as "me–too" drugs) may be promptly accomplished through one–off transactional relationships.*

4.4.5 Greatest Value from Strategic Partnership

Thus far, we have shown that there is a preference for strategic partnerships in the majority of cases. This then begs the question: in which environment does a strategic partnership offer the greatest advantage over a transactional arrangement? A central finding of the model is that in a particular environment (given in Theorem 2) the value created from a strategic partnership is threefold. That is, moving from a transactional arrangement to a strategic partnership results in the largest reduction in duration and offers the largest gain to the pharma company while also offering the CRO a higher payoff. This occurs in a low fine ($\alpha < K_A$) and low fixed payment ($F < 2K_A + fd(s_A, 0) - \alpha$) environment, given that the pharma company has a credible termination strategy ($d_o < d(s_B, 1) < d(s_B, 0)$ and $e < \phi_j \delta$) and that the exit fee is not lucrative for the CRO ($e < F + \alpha - 2K_A - fd(s_A, 1)$); this scenario corresponds to Eq. 22 for both types and Eq. 15, 16 for the strong type in Theorem 1.

THEOREM 2 **(Greatest value from a strategic partnership).** *In the environment characterized by Eq. 22 for both types and Eq. 15, 16 for the strong type, commitment offers*

(i) the highest reduction in duration, reducing the duration of both projects ($d_1(s_A, 1) < d_1(s_B, 0)$ and $d_2(s_A, 1) < d_o$),

(ii) the largest total gain in payoffs for the pharmaceutical company, and

(iii) a higher payoff for the CRO.

We have shown that in transactional relationships, when the CRO knows that a "B" team will not be rehired for future business (i.e., no prospect of repeat business) and stands to receive large fixed payments, it deploys its "A" team. However, when the CRO knows that a "B" team will be rehired (i.e., anticipation of repeat business), it deploys its "A" team in a high fine environment. Theorem 2 shows that in strategic partnerships, as opposed to transactional relationships, pharma companies do not need to make large fixed payments to CROs to reduce duration, nor do they need to heavily penalize their outsourcing partners through high fines. Thus, a strategic partnership is preferred when CRO performance cannot be ensured (due to low fixed payments and low fines) in a transactional relationship.

The pharma company, in this context, can instead incentivize "A" team deployment through committing future business to the CRO. Still, to avert the possible complacency problem that may arise from granting "strategic partner" status to the CRO, the pharma company needs to have a credible threat to terminate the partnership. The CRO knows that if it deploys its less capable "B" team, the pharma company will break its commitment and pay the CRO a small exit fee. Thus, the CRO chooses to deploy its "A" team instead.

In this scenario, project duration is substantially reduced since the "A" team works on both projects. (Had a transactional relationship been pursued, the "B" team would work on project 1 and the outside option would execute project 2, where $d_o > d(s_A, 1)$). Duration of both projects is further reduced by the planning flexibility that the CRO gains through commitment (w). Thus, the reduction in duration from a strategic partnership is twofold: commitment drives the CRO to

deploy its "A" team and also offers a gain from commitment. Subsequently, both players earn higher payoffs. By Lemma 1, this results in a substantially higher payoff for the pharma company for each project since $d(s_A, 1) < d_o < d(s_B, 0)$. The CRO also stands to earn a higher payoff in a strategic partnership since a "committed A" team for both projects earns a higher payoff than an "uncommitted B" team that completes project 1 but is not rehired for project 2.

4.5 Asymmetric Information Case

We next present the results of the asymmetric information model. In this case, the CRO is unsure of the pharma company's type since the CRO does not have transparency of the maximum revenue potential of the pharma company's projects, m_j. We find the perfect Bayesian equilibria (PBE) of the game.

Recall that Table 4.3 characterizes the SPNE for the full information game. For instance, Eq. 1 in Table 4.3 specifies the SPNE where the outside option is not viable and the fine environment is high. The SPNE is: both types of pharma company commit, a CRO deploys its "A" team if the pharma company commits, and both types maintain commitment to the "A" team. Under the same environment in the asymmetric information case, the equilibrium strategy is the same since it is not dependent on the pharma company's type. In Table 4.3 there are nine environments where the outcome is different for the weak and strong types of pharma company. Of these nine environments, we observe that there are only four (Eq. 12, 14–16) in which the CRO's best response differs based on whether they are working with the strong or weak pharma company. Therefore, in comparing the results of the full information model and the asymmetric model, we limit our discussion to these four environments; in other words, we consider only those environments in which transparency results in different outcomes and payoffs for the CRO and pharma company.

4.5.1 Stage 3: Maintain or Terminate the Relationship with the CRO?

From Corollary 1, we observe that when the CRO deploys its "A" team, the pharma company maintains the relationship (whether it be a transactional arrangement or strategic partnership). As

in the full information case, under asymmetric information, when the CRO deploys its "B" team in a transactional relationship, the pharma company's decision depends on the capability of the "B" team and the outside option. In a strategic partnership, the pharma company's decision is also influenced by the exit fee. The pharma's best response is the same as in the full information case and is given in Proposition 1.

Note that according to Proposition 1, in a transactional relationship, the CRO is rehired when $d_o > d(s_B, 0)$ and is not rehired when $d_o < d(s_B, 0)$, irrespective of whether the pharma company has a strong or a weak portfolio (i.e., both types take the same action). However, in a strategic partnership, the pharma company's type does have an impact on its decision. When the exit fee is quite small ($e < \phi_W \delta$), quite large ($e > \phi_S \delta$) or when the outside option is poor ($d_o > d(s_B, 1)$), both types take the same action. Yet, when the outside option is preferable to the "B" team ($d_o < d(s_B, 1)$) and the exit fee is prohibitive for a pharma company with a weak portfolio but not for one with a strong portfolio ($\phi_W \delta < e < \phi_S \delta$), the weak type and the strong type will diverge in their actions in the third stage.

4.5.2 Stage 2: CRO's Team Deployment Decision – "A" Team or "B" Team?

The reason why the equilibrium strategies under full information and asymmetric information scenarios are largely the same across environments (in all but four cases) becomes apparent when evaluating the CRO's team deployment decision. We find that when the strong and weak type pharma companies take the same actions in the third stage, the CRO receives the same payoff regardless of whether the pharma company's portfolio is strong or weak. Thus, when both types take the same actions in the third stage, it does not matter to the CRO whether it works with a pharma company with a weak or strong portfolio, and the best response of the CRO is given in Proposition 2. This holds true in a transactional relationship, both when it is preferable for either type of pharma company to maintain the strategic partnership and when it is preferable for either type to terminate the strategic partnership. The CRO's payoff does, however, vary when the actions taken by each type in the third stage are different. When $d_o < d(s_B, 1)$ and $\phi_W \delta < e < \phi_S \delta$, the CRO anticipates that a pharma company with a weak portfolio maintains its commitment whereas one with a strong portfolio breaks its commitment. In the former case, the CRO works on both

projects since the relationship is maintained, whereas in the latter case, the CRO only executes the first project.

Let

$$\bar{b} = \frac{\overbrace{\Pi_1^C(d_1(s_B,1)) + \Pi_2^C(d_2(s_B,1)) - \Pi_1^C(d_1(s_A,1)) + \Pi_2^C(d_2(s_A,1))}^{\text{(commit, "B" team, honor) – (commit, "A" team, honor)}}}{\underbrace{\Pi_2^C(d_2(s_B,1)) - e}_{\text{(commit, "B" team, honor) – (commit, "B" team, terminate)}}}, \quad (2)$$

Where $\bar{b}$ is the ratio of the difference in CRO's payoffs under a maintained relationship with its "B" team and its "A" team to the difference in CRO's payoffs under a maintained and terminated relationship with its "B" team.

Proposition 3 captures the CRO's team deployment decision when the CRO faces uncertainty regarding its partner's type and anticipates that only a pharma company with a strong project portfolio will break its commitment to the "B" team.

> PROPOSITION 3 **(Deploy "A" or "B" team when only strong pharma company has a credible threat?).** *In a strategic partnership, when only the strong type pharmaceutical company terminates the relationship following "B" team deployment, the CRO will deploy its "A" team if*
> *i.* $\alpha > K_A$, $F + \alpha - 2K_A - fd(s_A,1) > e$, *and* $0 \leq b \leq 1$.
> *ii.* $\alpha > K_A$, $F + \alpha - 2K_A - fd(s_A,1) < e$ *e, and* $0 \leq b < \bar{b}$.
> *iii.* $\alpha < K_A$, $F + \alpha - 2K_A - fd(s_A,1) > e$, *and* $\bar{b} < b \leq 1$,
> *and will deploy its "B" team otherwise.*

Under high fines and a low exit fee (Proposition 3(i)), the CRO's best response for any $0 \leq b \leq 1$ is to deploy its "A" team since the payoff it earns under a maintained relationship with its "A" team is higher than the payoff earned through a maintained or terminated relationship with its "B" team. Under high fines and a high exit fee (Proposition 3(ii)), the CRO stands to earn a higher payoff through deploying its "B" team rather than its "A" team when working with a strong type

but faces a smaller payoff with its "B" team versus its "A" team when employed by a weak type. If the CRO believes there is a low chance that the pharma company is strong (i.e., $0 \leq b < \bar{b}$), its best response is to deploy its "A" team. Conversely, under low fines and a low exit fee (Proposition 3(iii)), the CRO stands to earn a higher payoff through deploying its "B" team rather than its "A" team if working with a weak type but will get a smaller payoff via its "B" team when working with a strong type. Thus, if the CRO believes there is a high chance that the pharma company is strong (i.e., $\bar{b} < b \leq 1$), its best response is to deploy its "A" team.

4.5.3 Transparency regarding the Strength of the Project Portfolio?

In what follows, we only discuss the environments in which there is a difference between the equilibrium strategies of the full information model and the asymmetric information model; in other words, we discuss the environments where transparency impacts the companies' actions and payoffs. In these environments, $d_o < d(s_B, 1)$ and $\phi_W \delta < e < \phi_S \delta$ (thus the weak type and strong type pharma companies differ in their third stage actions) and the CRO's best response is captured in Proposition 3.

4.5.3.1 Low Fine and Low Exit Fee Environment

We first discuss the differences between the full information model and the asymmetric information model in low fine ($\alpha < K_A$) and low exit fee ($e < F + \alpha - 2K_A - fd(s_A, 1)$) environments. These environments can be further characterized by high fixed payments ($F > 2K_A + fd(s_A, 0) - \alpha$) or low fixed payments ($F < 2K_A + fd(s_A, 0) - \alpha$) and a high ($w > d_2(s_B, 1) - d_o$) or low ($w < d_2(s_B, 1) - d_o$) effectiveness of commitment. Figure 4.3 depicts the PBEs under asymmetric information and SPNEs under full information.

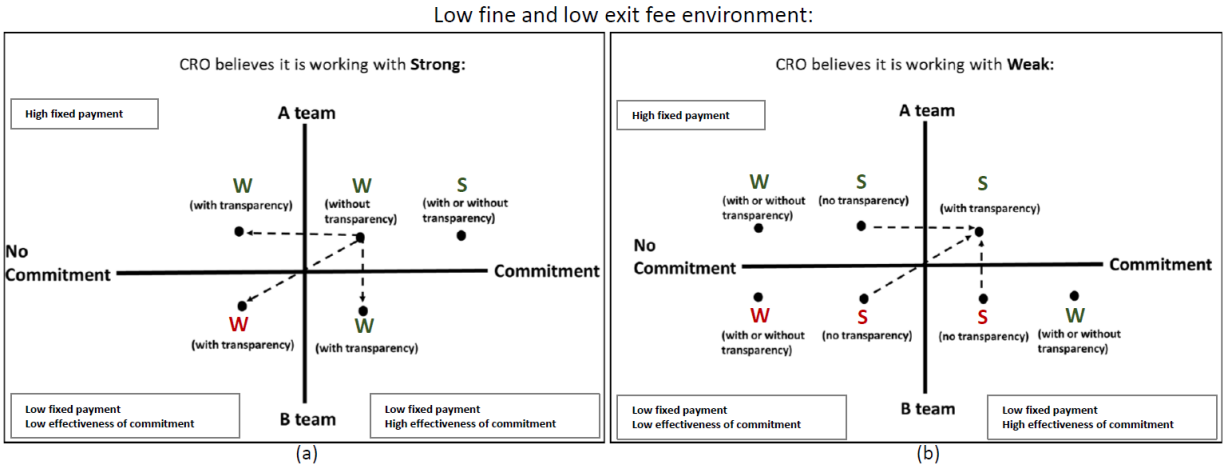

Figure 4.3 (a) Loss from transparency for weak type, (b) Gain from transparency for strong type. Consider (a). The equilibrium strategy for the strong type does not change with or without transparency: the pharma company commits, the CRO offers the "A" team, and the pharma company maintains the relationship (green). However, for the weak type, the strategy is different with or without transparency. For example, in a setting with low fixed payments and a low effectiveness of commitment, the weak type would end up with commitment and a maintained relationship with the "A" team without transparency (upper right quadrant) while, with transparency, the strategy would be no commitment, the "B" team, and a terminated relationship (red) (lower left quadrant).

First, consider the full information case. Under transparency, the CRO's beliefs do not matter and both panels provide the same observations. In equilibrium, under a low fine and low exit fee environment, the strong type commits to a CRO's "A" team and maintains the relationship (upper right quadrant in Figure 4.3 (a) and (b)). The weak type's decision also depends on other factors. In an environment further characterized by a high fixed payment (upper left quadrant in (a) and (b)), the weak type does not commit but maintains a transactional relationship with the CRO's "A" team in equilibrium. However, under a low fixed payment and low effectiveness of commitment environment (lower left quadrant in (a) and (b)), the weak type does not commit, the CRO assigns its "B" team and the weak type terminates the relationship in equilibrium. Finally, under a low fixed payment and high effectiveness of commitment environment (lower right quadrant in (a) and (b)), the weak type commits to the CRO's "B" team and maintains the relationship in equilibrium.

Let us now restrict ourselves to a low fine, low exit fee and high fixed payment environment and consider the asymmetric information situation. Without transparency, in this environment two pooling PBEs exist and depend on the CRO's belief regarding the pharma company's type. In the first PBE (Figure 4.3(a)), both types of pharma company choose to pool on commitment (upper right quadrant). If the CRO's belief lies in the range $\bar{b} < b \leq 1$, its best response is to deploy an "A" team since the strong type can credibly terminate the partnership and exit fees are low (Proposition 3(iii)). Both types of pharma company maintain the relationship. Unlike in the SPNE, transparency does not provide any value to the strong type (i.e., equilibrium strategy under full information is the same as asymmetric information). However, with transparency, the weak type does not commit (since the CRO deploys its "B" team in a strategic partnership as it is a low fine environment). As the fixed payment is high, the CRO deploys its "A" team in a transactional arrangement. Therefore, the weak type is worse off with transparency (in other words, the pharma company loses the benefit of commitment).

In the second PBE (Figure 4.3(b)), both types of the pharma company choose to pool on a transactional arrangement (upper left quadrant). If the CRO's belief lies in the range $0 \leq b < \bar{b}$, its best response in a strategic partnership is to deploy its "B" team as the weak type maintains the partnership and fines are low (Proposition 3(iii)). In contrast, in a transactional arrangement, the CRO deploys an "A" team due to high fixed payments. Unlike in the SPNE, transparency does not provide any value to the weak type (i.e., equilibrium strategy under full information is the same as asymmetric information). However, with transparency, the strong type commits. Since the strong type can credibly break its commitment and exit fees are low, the CRO deploys its "A" team following commitment. Therefore, the strong type is better off with transparency (gets the "A" team *and* the added benefit of commitment).

Theorem 3 extends this observation to all three environments (high fixed payment, low fixed payment with low effectiveness of commitment, and low fixed payment with high effectiveness of commitment) and shows that, under low fines and low exit fees, transparency can be advantageous for a pharma company with a strong portfolio and disadvantageous for a pharma company with a weak portfolio when only the strong type can make a credible threat to break its commitment ($\phi_W \delta < e < \phi_S \delta$).

THEOREM 3 **(Transparency can benefit the strong type and hurt the weak type).** *When* $d_o < d(s_B, 1)$, $\phi_W \delta < e < \phi_S \delta$, $\alpha < K_A$ *and* $e < F + \alpha - 2K_A - fd(s_A, 1)$, *a strong [weak] pharmaceutical company is*

• *no worse off [worse off] offering transparency to the CRO if* $\bar{b} < b \leq 1$;

• *better off [no better off] offering transparency to the CRO if* $0 \leq b < \bar{b}$.

We note that the strong type stands to make the largest gain (and equivalently, the weak type stands to suffer the largest loss) from transparency when fixed payments and the effectiveness of commitment are both low (Figure 4.3(b) and (a), respectively). This is because when fixed payments are high, the CRO deploys its "A" team even without commitment. Transparency thus offers the strong type the *additional benefit of reducing duration from commitment* (move from left to right on Figure 4.3(b)). On the other hand, when fixed payments are low but the effectiveness of commitment is high, the pharma company prefers to commit. Transparency benefits the strong type if makes it clear to the CRO that its portfolio is not weak. In such case, the CRO deploys its "A" team and transparency offers the *additional benefit of a more capable team* (upward move on Figure 4.3(b)). Under low fixed payments and a low effectiveness of commitment, transparency offers the strong type the *dual* benefit of a more capable team and of commitment (diagonal move on Figure 4.3 (b)). Following similar reasoning, Figure 4.3(a) shows that transparency results in the largest loss for a weak type pharma company.

4.5.3.2 High Fine and High Exit Fee Environment

Figure 4.4 depicts the SPNEs under full information and the PBEs under asymmetric information under a high fine and high exit fee environment. Interestingly, the figure shows that in high fine and high exit fee environments, transparency can benefit the weak type (Figure 4.4(a)) and hurt the strong type (Figure 4.4(b)) when only the strong type can make a credible threat of breaking its commitment (Theorem 4).

Figure 4.4. (a) Gain from transparency for weak type, (b) Loss from transparency for strong type. Consider (a). The equilibrium strategy for the strong type does not change with or without transparency: the pharma company does not commit, the CRO offers the "A" team, and the pharma company maintains the relationship (green). However, for the weak type, the strategies are different in the presence or absence of transparency. The weak type ends up with a transactional arrangement and a maintained relationship with the "A" team without transparency (upper left quadrant) while, with transparency, the equilibrium strategy would be commitment (i.e., strategic partnership), the "A" team, and a maintained relationship (upper right quadrant).

THEOREM 4 **(Transparency can hurt the strong type and benefit the weak type).** *When* $d_o < d(s_B, 1)$, $\phi_W \delta < e < \phi_S \delta$, $\alpha < K_A$ *and* $e < F + \alpha - 2K_A - fd(s_A, 1)$, *a strong [weak] pharmaceutical company is*

- *no worse off [better off] offering transparency to the CRO if* $\bar{b} < b \leq 1$;
- *worse off [no better off] offering transparency to the CRO if* $0 \leq b < \bar{b}$.

In examining the pharma company's transparency decision, much like Song et al. (2021), we find certain environments in which information asymmetry regarding the revenue potential of the pharma company's projects is preferable to full information, depending on the pharma company's portfolio strength. This indicates that although CROs often see transparency of the pharma company's pipeline potential as vital to their operations, *strategic partnerships can still be effective in reducing trial duration without transparency*. However, we also demonstrate that there are situations where transparency does benefit pharma companies with strong portfolios, and

counterintuitively, there are situations where transparency benefits companies with weak portfolios. In an environment characterized by low fines and low exit fees, a pharma company with a strong portfolio would like to be transparent with the CRO regarding its type so that it displays a credible threat of breaking its commitment (which would result in low CRO compensation) if the CRO deploys its "B" team (Theorem 3). On the other hand, in an environment marked by high fines and high exit fees, a pharma company with a weak portfolio prefers to be transparent regarding its portfolio strength to indicate to the CRO that it cannot credibly terminate the partnership following "B" team deployment. Knowing that commitment will be maintained (and a high compensation will not be paid out), team deployment is governed by high fines (Theorem 4). Thus, there are instances where the pharma company should be upfront with the CRO regarding the strength of its projects, even if projects have weak revenue potential, as this gives the CRO insight regarding how it will be treated in the relationship. We thus offer analytical evidence of the value of transparency in strategic partnerships.

4.6 Managerial Implications

Much has been written in the past few years about the challenges faced by the pharma industry: skyrocketing R&D costs, persistently high failure rates in the approval of new drugs, and the ever–increasing duration of and complexity in the design and execution of clinical trials. Yet recent developments in the industry, including the proliferation of healthcare technologies (Betcheva et al. 2021) and the unprecedented speed of development of the COVID–19 vaccines (Levy 2021), demonstrate that some of those assumptions (e.g., the decade–long bench–to–bedside development time) might not be as robust as we thought. Indeed, several industry executives have described this as a teachable moment in regard to how collaboration and alignment in the strategic priorities of different parties can accelerate drug development. For instance, the strategic partnership between Pfizer and ICON enabled ICON to recruit more than 44,000 trial participants in 153 sites around the globe in just four months for the Pfizer and BioNTech COVID–19 vaccine Phase 3 study (ICON plc 2021). However, our interviews with senior pharma and CRO executives point to several inefficiencies that prevent pharma–CRO relationships from maximizing their potential. This paper aims to shed light on the drivers of successful relationships and develop a framework

for overcoming the current inefficiencies. In this section, we discuss the managerial implications of these results.[13]

Initially providing spillover capacity, CROs have recently gained prominence by offering advantages in speed, efficiency, and accuracy in the design and execution of clinical trials (Shuchman 2007). The growing competence and capabilities of the CRO industry are reflected in the industry market size: estimated at $50.09 billion in 2021, the CRO market is expected to grow to $88.83 billion by 2028 (Insight Partners Study 2021). Interestingly, although the tasks and responsibilities of the two parties have significantly changed over the past decade, it appears that relationship models have been slow to adapt. Most pharma–CRO relationships are still characterized by a process similar to a reverse auction and a reliance on transactional contract terms that emphasize zero–sum monetary terms rather than drivers of joint value creation.

Our analysis reinforces the notion that such transactional arrangements are often inadequate to address the challenges of the rising complexity of clinical trials. At the same time, executives are generally reluctant to replace such transactional models, given the lack of clarity as to what constitutes a strategic partnership. This is stressed by Azoulay et al. (2010), who argue that there is usually a gap between what is promised from a committed relationship and what is actually delivered. Issues jeopardizing the value attained from strategic partnerships include unclear expectations, role ambiguity leading to unnecessary duplication of tasks, and micromanagement by clients (Quintiles 2013, Hughes and Price 2016), to name a few. That is why, in suggesting a strategic partnership model, one needs to carefully consider the operational details (e.g., termination options) and the conditions that satisfy those (e.g., credible threat of termination).

The two key managerial implications from our analysis relate to the *when* and *how* of strategic partnerships. That is, our first set of results demonstrates why transactional arrangements might fail to create value in a wide range of environments and when strategic partnerships can overcome those hurdles. Recall that transactional arrangements are preferable in environments where one of

[13] We note that, although our focus is on the pharma industry, our insights may offer guidance and may be extended to other industries such as consulting, where similar to clinical development, projects are complex and knowledge intensive, duration is often of the utmost importance and incumbents face the strategic decision regarding the type of outsourcing relationship to pursue with their vendors.

the following conditions is met: i) high fixed payments (not ideal for the pharma company) or ii) high fine terms (not desirable for the CRO). However, in light of new trial designs (e.g., adaptive, basket, umbrella clinical trials) and new types of therapies (e.g., gene and cell therapy), it is clear that arrangements that require steep and rigid monetary payments or penalties are not suitable for those novel approaches that require flexibility and adaptation. Instead, a strategic partnership with a well–structured termination strategy enables incentive alignment (where the CRO brings the "A" team) devoid of high payments and high fines. That is why our analysis suggests that there are more environments conducive to strategic partnerships than environments conducive to transactional arrangements (especially for pharma companies with strong pipelines). This balance is also reflected in the increasing shift towards partnering–focused relationship models within the industry in recent years (Meyer 2015). However, there is still a place for transactional arrangements when the benefits of commitment are limited (e.g., for well–defined projects that do not necessitate a high degree of foresight and dialogue.)

Our work also offers suggestions as to how current industry practices can be reevaluated to enhance relationships. For instance, our analysis highlights a second key benefit of strategic partnerships: the presence of commitment bypasses the demands for more detailed information that may hinder the pharma–CRO relationship. Several industry reports note that a key concern for the CROs is the uncertainty regarding the importance of a given project in their clients' pipelines (e.g., how likely it is that the project may be suddenly deprioritized). As a result, our interviewees pointed out that CROs often call for full disclosure of the market revenue potential and importance of projects in the pharma company's pipeline, arguing that such information is critical to planning and managing their operations. Pharma companies rarely satisfy such requests, and these queries often become a major roadblock in the relationship. Our analysis shows that, in many cases, strategic partnerships can still be effective in reducing the trial duration without transparency. This is because the value of transparency stems from its ability to resolve unintended consequences of contracts (such as a project deprioritization), and, as we show, transparency adds no value to the relationship in many instances. This is especially worthwhile to consider given the time, cost and effort associated with the disclosure of market information (e.g., the legal burden of non–disclosure agreements). The pharma industry is not new to evolving relationship models. In

the early days of the biotechnology industry, pharma companies approached many of the smaller biotech companies in a purely transactional manner. The so–called "cash–and–carry" deals transferred full ownership (and control) to the pharma company in exchange for upfront cash and milestone payments. A number of academic studies, as well as industry case studies (e.g., Lerner et al. (2003)), have shown that contractual terms that only emphasize monetary levers are not appropriate in addressing the challenges associated with pharma projects (e.g., high levels of uncertainty, interdependency of activities, etc.). Pharma–biotech relationships eventually transformed into more collaborative initiatives. Strategic partnerships between these companies include all kinds of options, joint development and decision-making, as well as early–stage accelerators and incubators that provide free mentoring and facilities to biotech companies (see, e.g., JLABS[14]). However, this has been a long journey for the industry, spanning over three decades.

The extant academic literature has examined the relationships between pharma and biotech companies in great depth. However, research has overlooked the equally critical development ("D") part of the R&D process, which must similarly be transformed. Specifically, given continuing advances in therapeutics (such as gene and cell therapies), new digital technologies that allow for decentralized (remote) clinical trials, and new trial designs that aim to maximize efficiency (e.g., adaptive trials), the relationships between pharma companies and CROs need to be revisited. At a time when improving the efficiency of the drug development process is becoming ever more important, our results may assist pharma managers in identifying the right kind of outsourcing relationship for the type of environment they operate in. We hope that our work can begin to fill this gap and motivate other academic research focused on this growing and vibrant industry.

[14] *"JLABS provides the optimal environment for emerging companies to catalyze growth and optimize their research and development by opening them to vital industry connections, delivering entrepreneurial programs and providing a capital-efficient, flexible platform where they can transform the scientific discoveries of today into the breakthrough healthcare solutions of tomorrow... What that means for young companies is that, no matter what stage you're at, we provide access to all the elements you need to develop your science and to position your company for success"* (Johnson & Johnson Innovation 2022).

References

Adida, E., F. Bravo. 2019. Contracts for healthcare referral services: Coordination via outcome–based penalty contracts. *Management Science* 65(3):1322–1341.

Anderer, A., H. Bastani, J. Silberholz. 2021. Adaptive clinical trial designs with surrogates: When should we bother? *Management Science* 68(3):1962–2002.

Andritsos, D.A., C.S. Tang. 2018. Incentive programs for reducing readmissions when patient care is coproduced. *Production and Operations Management* 27(6):999–1020.

Azoulay, P., N.P. Repenning, E.W. Zuckerman. 2010. Nasty, brutish, and short: Embeddedness failure in the pharmaceutical industry. *Administrative Science Quarterly* 55(3):472–507.

Bayiz, M., C.J. Corbett. 2005. Coordination and incentive contracts in project management under asymmetric information. Working Paper Anderson Graduate School of Management, University of California, Los Angeles.

Betcheva, L., F. Erhun, H. Jiang. 2021. Supply chain thinking in healthcare: Lessons and outlooks. *Manufacturing & Service Operations Management* 23(6):1333–1353.

Bhattacharya, S., V. Gaba, S. Hasija. 2015. A comparison of milestone–based and buyout options contracts for coordinating R&D partnership. *Management Science* 61(5):963–978.

Bravo, F., T.C. Corcoran, E.F. Long. 2022. Flexible drug approval policies. *Manufacturing & Service Operations Management* 24(1):542–560.

Challener, C.A., C. Cao, E. Branch. 2017. Building strategic sponsor–CRO partnerships: The international element changing clinical trials. Pharma's Almanac. Available at: https://www.pharmasalmanac.com/articles/building–strategic–sponsor–cro–partnerships.

Chen, S., H. Lee. 2017. Incentive alignment and coordination of project supply chains. *Management Science* 63(4):1011–1025.

Chen, T., T. Klastorin, M.R. Wagner. 2015. Incentive contracts in serial stochastic projects. *Manufacturing & Service Operations Management* 17(3):290–301.

Cini, P. 2022. The talent shortage in biopharma demands a creative solution. Outsourced Pharma. Available at: https://www.outsourcedpharma.com/doc/the–talent–shortage–in–biopharma–demands–a–creative–solution–0001.

Crama, P., B. De Reyck, N. Taneri. 2017. Licensing contracts: Control rights, options, and timing. *Management Science* 63(4):1131–1149.

Credevo. 2021. How to choose a CRO?: Small and mid–size pharma companies. Available at: https://credevo.com/articles/2019/08/16/how–to–choose–a–cro–small–mid–size–pharma–companies/.

Davis, A.M., K. Hyndman. 2018. An experimental investigation of managing quality through monetary and relational incentives. *Management Science* 64(5):2345–2365.

Dawande, M., G. Janakiraman, A. Qi. 2019. Optimal incentive contracts in project management. *Production and Operations Management* 28(6):1431–1445.

DiMasi, J.A., H.G. Grabowski, R.W. Hansen. 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics* 47(May):20–33.

Drakeman, D.L., Drakeman L.N., N. Oraiopoulos. 2022. *From Breakthrough to Blockbuster: The Business of Biotechnology*. Oxford University Press Inc., New York, United States of America.

Economist Intelligence Unit. 2012. Finding alignment: Opportunities and obstacles in the pharma/CRO relationship. *The Economist.* Available at: https://www.yumpu.com/en/document/read/37736329/finding–alignment–opportunities–and–obstacles–in–the–pharma–cro–.

Eid, S. 2020. Tips for establishing & maintaining an effective CRO partnership. *Clinical Leader.* Available at: https://www.clinicalleader.com/doc/tips–for–establishing–maintaining–an–effective–cro–partnership–0001.

Elvidge, S. 2015. The evolution of CRO reimbursement: Shifting from task–driven units to desired outputs. *Life Science Leader* Available at: https://www.lifescienceleader.com/doc/the–evolution–of–cro–reimbursement–shifting–from–task–driven–units–to–desired–outputs–0001.

Evotec. 2022. Five factors to consider when selecting the right CRO for your drug development program. Available at: https://news.evotec.com/five–factors–to–consider–when–selecting–the–right–cro–for–your–drug–development–program.

Fassbender, M. 2019. CRO industry still plagued by CRA turnover: Report. *Outsourced Pharma.* Available at: https://www.outsourcing–pharma.com/Article/2019/01/03/CRO–industry–still–plagued–by–CRA– turnover–Report.

Haeussler, C., B. Rake. 2017. The changing geography of clinical research: A critical analysis of its drivers. *Industrial & Corporate Change* 26(2):285–310.

Hargreaves, B. 2016. Clinical trials and their patients: The rising costs and how to stem the loss. *Pharmafile.* Available at: http://www.pharmafile.com/news/511225/clinical–trials–and–their–patients–rising–costs–and–how–stem–loss.

Hatcher, A., J. Hughes. 2016. Applying best practices from other industries to sponsor–CRO relationships. *Pharmaceutical Outsourcing.* Available at: https://www.pharmoutsourcing.com/Featured–Articles/182575–Applying–Best–Practices–from–Other–Industries–to–Sponsor–CRO–Relationships/.

Hughes, J., S. Price. 2016. The perils and promise of strategic partnering with CROs. *Pharmaceutical Outsourcing.* Available at: https://www.pharmoutsourcing.com/Featured–Articles/184119–The–Perils–and–Promise–of–Strategic–Partnering–with–CROs/.

Hyndman, K., D. Honhon. 2020. Flexibility in long–term relationships: An experimental study. *Manufacturing & Service Operations Management* 22(2):273–291.

ICON plc. 2021. Press Release. Available at: https://www.iconplc.com/news–events/press–releases/icon–pfizer– biontech/.

Jiang, H., Z. Pang, S. Savin. 2012. Performance–based contracts for outpatient medical services. *Manufacturing & Operations Management* 14(4):654–669.

Johnson & Johnson Innovation. 2022. Vision. Available at: https://jlabs.jnjinnovation.com/vision.

Kouvelis, P., J. Milner, Z. Tian. 2017. Clinical trials for new drug development: Optimal investment and application. *Manufacturing & Service Operations Management* 19(3):437–452.

KPMG. 2012. Outsourcing in the pharmaceutical industry: 2011 and beyond. *KPMG LLP*. Available at: https://kpmg.ca/biotechandpharma.

Kwon, H.D., S.A. Lippman, K.F. McCardle, C.S. Tang. 2010a. Project management contracts with delayed payments. *Manufacturing & Service Operations Management* 12(4):692–707.

Kwon, H.D., S.A. Lippman, C.S. Tang. 2010b. Optimal time–based and cost–based coordinated project contracts with unobservable work rates. *International Journal of Production Economics* 126(2): 247–254.

Ledesma, P. 2020. How to select a clinical research organization (CRO). Sofpromed. Available at: https://www.sofpromed.com/how–to–select–a–clinical–research–organization–cro.

Lerner, J., H. Shane, A. Tsai. 2003. Do equity financing cycles matter? Evidence from biotechnology alliances. *Journal of Financial Economics* 67(3):411–446.

Levy, V. 2021. 2021 global life sciences outlook: Possibility is now reality, sustaining forward momentum. *Deloitte Insights.* Available at: https://www2.deloitte.com/cn/en/pages/life–sciences–and–healthcare/articles/global–life–sciences–outlook–2021.html.

Mahan, V.L. 2014. Clinical trial phases. *International Journal of Medicine* 5:1374–1383.

Mclaren, M. 2021. Solving clinical trial delays: Three things to do now. Pharmaceutical Technology. Available at: https://www.pharmaceutical–technology.com/sponsored/solving–clinical–trial–delays/.

Meyer, J. 2015. Blog article on future of biopharmaceutical outsourcing. *Life Science Strategy Group.* Available at: https://www.outsourcepharma.com/tag/life–science–strategy–group/.

Nadarajah, S. 2017. The evolution of the pharma–CRO working relationship: AstraZeneca and Covance. *Bioanalysis* 9(15):1171–1174.

Nice Insight Preclinical and Clinical Contract Research Survey. 2017.

Personal Communication. 2020. In–person and phone interviews with professionals from pharmaceutical companies and CROs.

PhRMA. 2016. 2016 profile: Biopharmaceutical research industry. Pharmaceutical Research and Manufacturers of America. Available at: http://phrma–docs.phrma.org/sites/default/files/pdf/biopharmaceutical–industry–profile.pdf.

Prior, K. 2015. Ensuring in–depth planning takes place within trial supply to meet the demands of the globalization of clinical studies. Clinical Trial Yearbook 2015. Available at: http://viewer.zmags.com/publication/37ab9aac#/37ab9aac/1.

Quintiles. 2013. Sponsor/CRO partnership optimization. Quintiles. Available at: https://www.iqvia.com/–/media/library/white–papers/sponsor–cro–partnership–optimization.pdf?vs=1.

Rahmani, M., G. Roels, U.S. Karmarkar. 2017. Collaborative work dynamics in projects with co–production. *Production and Operations Management* 26(4):686–703.

Results Healthcare. 2013. CROs and other outsourced pharmaceutical support services: M&A drivers and trends. Results Healthcare. Available at: https://www.resultshealthcare.com/news–insights/white–papers/cro–white–paper?_sp=4fae9213–f59f–4131–ac8f–723974db88f9.1645528956887.

Roels, G. 2014. Optimal design of coproductive services: Interaction and work allocation. *Manufacturing & Service Operations Management* 16(4):578–594.

Savva, N., S. Scholtes. 2014. Opt–out options in new product co–development partnerships. *Production and Operations Management* 23(8):1370–1386.

Schultz, J. 2013. CRO strategic partnerships. *Contract Pharma.* Available at: https://www.contractpharma.com/issues/2013–03/view_features/cro–strategic–partnerships.

Shuchman, M. 2007. Commercializing clinical trials– risks and benefits of the CRO boom. *The New England Journal of Medicine* 357(14):1365–1368.

Song, J.M., Y. Zhao, X. Xu. 2021. Incentives and gaming in collaborative projects under risk–sharing partnerships. *Manufacturing & Service Operations Management* 23(2):453–470.

Sykes, J. 2021. Overcoming pharma's talent scarcity challenges. *Pharmaceutical Executive.* Available at: https://www.pharmexec.com/view/overcoming–pharma–s–talent–scarcity–challenges.

Taneri, N., A. De Meyer. 2017. Contract theory: Impact on biopharmaceutical alliance structure and performance. *Manufacturing & Service Operations Management* 19(3):453–471.

Tian, Z., H. Gurnani, Y. Xu. 2021. Collaboration in development of new drugs. *Production and Operations Management* 30(11):3943–3966.

Tian, Z., W. Han, W.B. Powell. 2022. Adaptive learning of drug quality and optimization of patient recruitment for clinical trials with dropouts. *Manufacturing & Service Operations Management* 24(1):580–599.

Vairaktarakis, G.L. 2013. Noncooperative games for subcontracting operations. *Manufacturing & Service Operations Management* 15(1):148–158.

Walker, N. 2015. Building a successful CMO/CRO partnership: What's important to emerging pharma and emerging biotech? *Life Science Leader*. Available at: https://www.lifescienceleader.com.

Wright, R. 2014. The future of clinical trials in an outsourced model. *Clinical Leader*. Available at: http://www.clinicalleader.com/doc/the–future–of–clinical–trials–in–an–outsourced–model–0001.

Xiao, W., Y. Xu. 2012. The impact of royalty contract revision in a multistage strategic R&D alliance. *Management Science* 58(12):2251–2271.

Zhang, D.J., I. Gurvich, J.A. Van Mieghem, E. Park, R.S. Young, M.V. Williams. 2016. Hospital readmissions reduction program: An economic and operational analysis. *Management Science* 62(11): 3351–3371.

Appendix

4.A Proofs

Proof of Lemma 1: Let $\underline{d}$ be the duration for the capable option and $\bar{d}$ be the duration for the less capable option; $\underline{d} < \bar{d}$. Recall $\Pi_{i,j}^{P} = R_{i,j}(d_i) - T_i(d_i) = m_j(1 - ld_i) - (F - fd_i)$. Then, the difference between the pharma company's payoffs for a project with the capable option and the less capable option is as follows:

$$\Pi_{i,j}^{P}(\underline{d}) - \Pi_{i,j}^{P}(\bar{d}) = m_j l(\bar{d} - \underline{d}) - f(\bar{d} - \underline{d}) = (m_j l - f)(\bar{d} - \underline{d}).$$

Since $m_j l > f$, this difference is positive, and the pharma company prefers the *more* capable outsourcing option (resulting in a lower duration).

**Note: Lemma 1 considers a project's gross profit not factoring in the exit fee. When $h = 0$ (i.e., the partnership is terminated for the pursuit of the outside option and the CRO is paid an exit fee), the pharma company's payoff with the capable option is $\Pi_{2,j}^{P} = R_{2,j}(\underline{d}) - T_2(\underline{d}) - e = m_j(1 - l\underline{d}) - (F - f\underline{d}) - e$. Since $e > 0$, the pharma company may or may not prefer the more capable outsourcing option.* ■

Proof of Corollary 1: Since the CRO's "A" team is the most capable outsourcing option for the pharma company, the corollary follows straightforwardly from Lemma 1. ■

Proof of Proposition 1: To find the subgame perfect Nash equilibrium (SPNE), we use backward induction and start with the pharma company's stage 3 decision (Figure 4.1).

Recall $\Pi_{i,j}^{P} = R_{i,j}(d_i) - T_i(d_i) = m_j(1 - ld_i) - (F - fd_i)$. By Lemma 1, $\Pi_{i,j}^{P}$ is decreasing in d_i. In a transactional relationship ($c = 0$), if the CRO deploys its "B" team, the pharma company faces a payoff of $\Pi_{2,j}^{P}(d_2(s_B, 0))$ with the CRO's "B" team or a payoff of $\Pi_{2,j}^{P}(d_o)$ with the

outside option for the second project. In a strategic partnership ($c = 1$), if the CRO deploys its "B" team, the pharma company faces a payoff of $\Pi_{2,j}^{P}(d_2(s_B, 1))$ with the CRO's "B" team or $\Pi_{2,j}^{P}(d_o) - e$ with the outside option for the second project.

In a transactional arrangement, by Lemma 1, when $d_o > d(s_B, 0)$, the pharma company's best response is to rehire the "B" team. Similarly, when $d_o < d(s_B, 0)$, the pharma company's best response is to employ the outside option.

Under a strategic partnership, when $d_o > d(s_B, 1)$, the pharma company's best response is to maintain the relationship with the "B" team. When $d_o < d(s_B, 1)$, although the pharma company would similarly rather use the more capable outside option, the exit fee may not allow for it. The pharma company should compare the gain in its payoff from pursing the outside option, $\Pi_{2,j}^{P}(d_o) - \Pi_{2,j}^{P}(d_2(s_B, 1))$, to the exit fee e:

$$\Pi_{2,j}^{P}(d_o) - \Pi_{2,j}^{P}\big(d_2(s_B, 1)\big) = m_j l(d_2(s_B, 1) - d_o) - f(d_2(s_B, 1) - d_o)$$
$$= (m_j l - f)(d_2(s_B, 1) - d_o)$$

Let $\phi_j = m_j l - f$ and $\delta = d_2(s_B, c) - d_o$. The pharma company maintains the relationship if the gain $\phi_j \delta$ is lower than e; i.e., $ec > \phi_j \delta$ even when $d_o < d(s_B, 1)$. On the other hand, the pharma company's best response is to break its commitment and pursue its outside option when $d_o < d(s_B, 1)$ and $ec < \phi_j \delta$.

Putting these results together, we show that when the CRO deploys its "B" team, the pharma company's best response is to (a) maintain the relationship with the "B" team either if $d_o > d(s_B, c)$ or if $d_o < d(s_B, c)$ and $ec > \phi_j \delta$; and (b) pursue its outside option $if\ d_o < d(s_B, c)$ and $ec < \phi_j \delta$. ■

Proof of Proposition 2: Given the pharma's stage 3 best response captured in Proposition 1, we now move onto the CRO's stage 2 team deployment decision. Recall $\Pi_i^C = F - f d_i - K_g$ and $K_B = 0$. If the CRO deploys its "A" team, by Corollary 1, the pharma company's best response is

to maintain the relationship resulting in a payoff for the CRO of $\Pi_1^C(d_1(s_A,c)) + \Pi_2^C(d_2(s_A,c))$, $c = \{0,1\}$. The CRO's team deployment choice can be one of two cases:

Case 1: When $d_o > d(s_B,c)$ or $d_o < d(s_B,c)$ and $ec > \phi_j\delta$, if the CRO deploys its "B" team, by Proposition 1(a), the pharma company maintains the relationship resulting in a payoff for the CRO of $\Pi_1^C(d_1(s_B,c)) + \Pi_2^C(d_2(s_B,c))$, $c = \{0,1\}$. The difference in CRO payoffs from deploying an "A" vs. a "B" team is

$$\begin{aligned}&\Pi_1^C\big(d_1(s_A,c)\big) + \Pi_2^C\big(d_2(s_A,c)\big) - \Pi_1^C(d_1(s_B,c)) + \Pi_2^C(d_2(s_B,c)))\\ =\ &(2F - f(d_1(s_A,c) + d_2(s_A,c)) - 2K_A) - (2F - f(d_1(s_B,c) + d_2(s_B,c)))\\ =\ &-2(K_A - fs_A + fs_B).\end{aligned}$$

Last equality follows as $d_i(s_g,c) = \tau - s_g - wc$. Recall $\alpha = f(s_A - s_B)$. The CRO deploys its "A" team when $\alpha > K_A$ and deploys its "B" team when $\alpha < K_A$.

Case 2: When $d_o < d(s_B,c)$ and $ec < \phi_j\delta$, if the CRO deploys its "B" team, by Proposition 1(b), the pharma company pursues its outside option resulting in a payoff for the CRO of $\Pi_1^C(d_1(s_B,c)) + ec$, $c = \{0,1\}$. The difference in CRO payoffs from deploying an "A" vs. a "B" team is

$$\begin{aligned}&\Pi_1^C\big(d_1(s_A,c)\big) + \Pi_2^C\big(d_2(s_A,c)\big) - \Pi_1^C(d_1(s_B,c)) + ec)\\ =\ &(2F - f(d_1(s_A,c) + d_2(s_A,c)) - 2K_A) - (F - fd_1(s_B,c) + ec)\\ =\ &F + fs_A - fs_B - 2K_A - fd_2(s_A,c) - ec\end{aligned}$$

Let $d(s_g,c) = d_1(s_g,c) = d_2(s_g,c)$. The CRO deploys its "A" team when $ec < F + \alpha - 2K_A - fd(s_A,c)$ and deploys its "B" team when $ec > F + \alpha - 2K_A - fd(s_A,c)$. ■

Proof of Theorem 1: Given Proposition 1 and Proposition 2, we characterize the pharma company's stage 1 decision and the SPNE of the game. There are 25 parameter combinations that we need to consider for the pharma company's commitment choice in stage 1. We analyze said combinations under 5 cases based on the duration of the outside option and the exit fee as follows:

Case I. Outside option not viable: When $d(s_B, 1) < d(s_B, 0) < d_o$, the pharma company rehires (keeps its commitment to) a "B" team if $c = 0$ ($c = 1$) by Proposition 1(a). Since fines govern the CRO in a maintained relationship, we consider two cases for the CRO:

(I.a) When $\alpha > K_A$, the CRO deploys an "A" team if $c = 0$ or $c = 1$ by Proposition 2(i). Recall $d_i(s_g, c) = \tau - s_g - wc$. By Lemma 1, $\Pi^P_{i,j}(d_i(s_A, 1)) > \Pi^P_{i,j}(d_i(s_A, 0))$. Thus, both types of pharma company commit to the CRO (Eq. 1 in Table 4.3).

(I.b) When $\alpha < K_A$, the CRO deploys a "B" team if $c = 0$ or $c = 1$ by Proposition 2(i). By Lemma 1, $\Pi^P_{i,j}(d_i(s_B, 1)) > \Pi^P_{i,j}(d_i(s_B, 0))$. Thus, both types of pharma company commit to the CRO (Eq. 2).

Case II. Bad outside option: When $d(s_B, 1) < d_o < d(s_B, 0)$, the pharma company does not rehire a "B" team if $c = 0$ by Proposition 1(b) and keeps its commitment to a "B" team if $c = 1$ by Proposition 1(a). Recall $T_i(d_i) = F - fd_i$. Note that, under insufficient fixed payments ($F < fd(s_B, 0)$), the heavily penalized CRO receives a negative transfer payment and therefore will not engage with the pharma company. Therefore, as illustrated in Figure 4.A.1 and based on the conditions in Proposition 2, there are three cases for the CRO depending on the values of α and F:

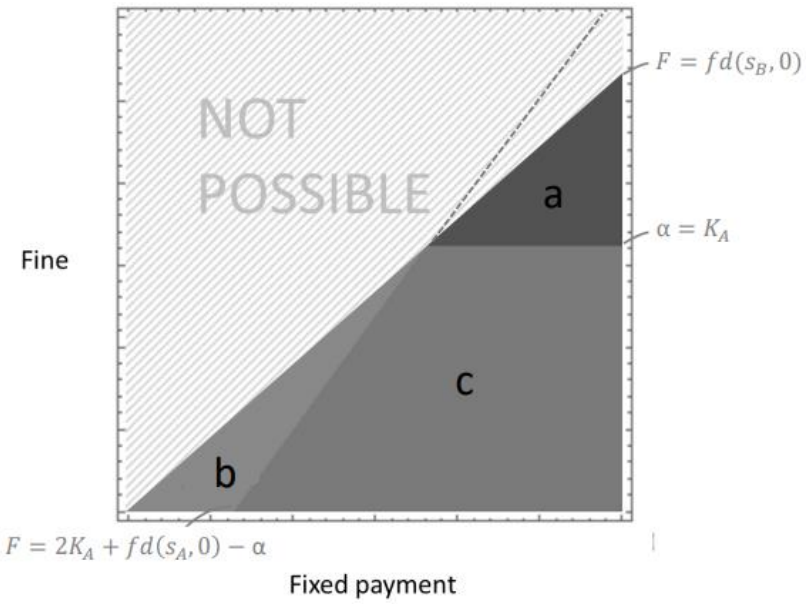

Figure 4.A.1 Three regions for Case II and Case III for the CRO based on the values of α and F under a bad outside option.

(II.a) Consider the case where $\alpha > K_A$. When $c = 1$, by Proposition 2(i), the CRO deploys an "A" team since the pharma company maintains the relationship in stage 3. When $c = 0$, by Proposition 2(ii), the CRO deploys an "A" team if $F + \alpha - 2K_A > fd(s_A, 0)$. Note that when $F > fd(s_B, 0)$, $F + \alpha - 2K_A - fd(s_A, 0) > fd(s_B, 0) + \alpha - 2K_A - fd(s_A, 0) = 2(\alpha - K_A) > 0$. Therefore, the CRO deploys an "A" team. By Lemma 1, $\Pi_{i,j}^P\big(d_i(s_A, 1)\big) > \Pi_{i,j}^P\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company commit to the CRO (Eq. 3).

(II.b) When $\alpha < K_A$ and $F < 2K_A + fd(s_A, 0) - \alpha$, the CRO deploys a "B" team if $c = 0$ ($c = 1$) by Proposition 2(ii) (Proposition 2(i)). By Lemma 1, $\Pi_{1,j}^P\big(d_1(s_B, 1)\big) > \Pi_{1,j}^P\big(d_1(s_B, 0)\big)$ and since $d_o > d(s_B, 1)$, $\Pi_{2,j}^P\big(d_2(s_B, 1)\big) > \Pi_{2,j}^P(d_o)$. Thus, both types of pharma company commit to the CRO (Eq. 4).

(II.c) When $\alpha < K_A$ and $F > 2K_A + fd(s_A, 0) - \alpha$, the CRO deploys an "A" ("B") team if $c = 0$ ($c = 1$) by Proposition 2(ii) (Proposition 2(i)).

- Recall $d_i(s_g, c) = \tau - s_g - wc$. If the effectiveness of commitment is larger than the marginal effectiveness of the "A" team, $w > s_A - s_B$, $d_i(s_B, 1) < d_i(s_A, 0)$. By Lemma 1 $\Pi_{i,j}^P\big(d_i(s_B, 1)\big) > \Pi_{i,j}^P\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company commit to the CRO (Eq. 5).
- If the effectiveness of commitment is smaller than the marginal effectiveness of the "A" team, $w < s_A - s_B$, $d_i(s_B, 1) > d_i(s_A, 0)$. By Lemma 1, $\Pi_{i,j}^P\big(d_i(s_B, 1)\big) < \Pi_{i,j}^P\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company do not commit to the CRO (Eq. 6).

Case III. Good outside option & high exit fees: When $d_o < d(s_B, 1) < d(s_B, 0)$ and $\phi_W\delta < \phi_S\delta < e$, the pharma company does not rehire (keeps its commitment to) a "B" team if $c = 0$ ($c = 1$) by Proposition 1(b) (Proposition 1(a)). Similar to Case II and as illustrated in Figure 4.A.1, based on the conditions in Proposition 2 there are three regions for the CRO depending on the values of α and F:

(III.a) Consider the case where $\alpha > K_A$. When $c = 1$, by Proposition 2(i), the CRO deploys an "A" team since the pharma company maintains the relationship in stage 3. When $c = 0$, by Proposition 2(ii), the CRO deploys an "A" team if $F + \alpha - 2K_A > fd(s_A, 0)$. Note that when $F > fd(s_B, 0)$, $F + \alpha - 2K_A - fd(s_A, 0) > fd(s_B, 0) + \alpha - 2K_A - fd(s_A, 0) = 2(\alpha - K_A) > 0$. Therefore, the CRO deploys an "A" team. By Lemma 1, $\Pi_{i,j}^P\big(d_i(s_A, 1)\big) > \Pi_{i,j}^P\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company commit to the CRO (Eq. 7).

(III.b) When $\alpha < K_A$ and $F < 2K_A + fd(s_A, 0) - \alpha$, the CRO deploys a "B" if $c = 0$ ($c = 1$) by Proposition 2(ii) (Proposition 2(i)).

- Recall $d_i(s_g, c) = \tau - s_g - wc$. The gain from commitment in the first period is $\Pi_{1,j}^P\big(d_1(s_B, 1)\big) - \Pi_{1,j}^P\big(d_1(s_B, 0)\big) = \big(m_j l - f\big)\big(d_1(s_B, 0) - d_1(s_B, 1)\big) = \big(m_j l - f\big)w$. The loss from not going with outside option in the second period is $\Pi_{2,j}^P(d_o) - \Pi_{2,j}^P\big(d_2(s_B, 1)\big) = \big(m_j l - f\big)(d(s_B, 1) - d_o)$. If $w > d_2(s_B, 1) - d_o$, the gain from the first period exceeds the loss from the second period. Thus, both types of pharma company commit to the CRO (Eq. 8).
- If $w < d_2(s_B, 1) - d_o$, the gain from commitment in the first period is less than the loss from not going with outside option in the second period. Thus, both types of pharma company do not commit to the CRO (Eq. 9).

(III.c) When $\alpha < K_A$ and $F > 2K_A + fd(s_A, 0) - \alpha$, the CRO deploys an "A" ("B") team if $c = 0$ ($c = 1$) by Proposition 2(ii) (2(i)). Since $d(s_A, 0) < d(s_B, 1) < d_o$, $w < s_A - s_B$ and thus $d_i(s_B, 1) > d_i(s_A, 0)$. By Lemma 1, $\Pi_{i,j}^P\big(d_i(s_B, 1)\big) < \Pi_{i,j}^P\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company do not commit to the CRO (Eq. 10).

Case IV. Good outside option & moderate exit fees: When $d_o < d(s_B, 1) < d(s_B, 0)$ and $\phi_W \delta < e < \phi_S \delta$, both types of pharma company will not rehire a "B" team if $c = 0$ by Proposition 1(b), the weak type keeps its commitment to the "B" team if $c = 1$ by Proposition 1(a), and the strong type breaks its commitment to the "B" team if $c = 1$ by Proposition 1(b). As illustrated in Figure 4.A.2, there are six cases for the CRO based on the values of α, F, and e:

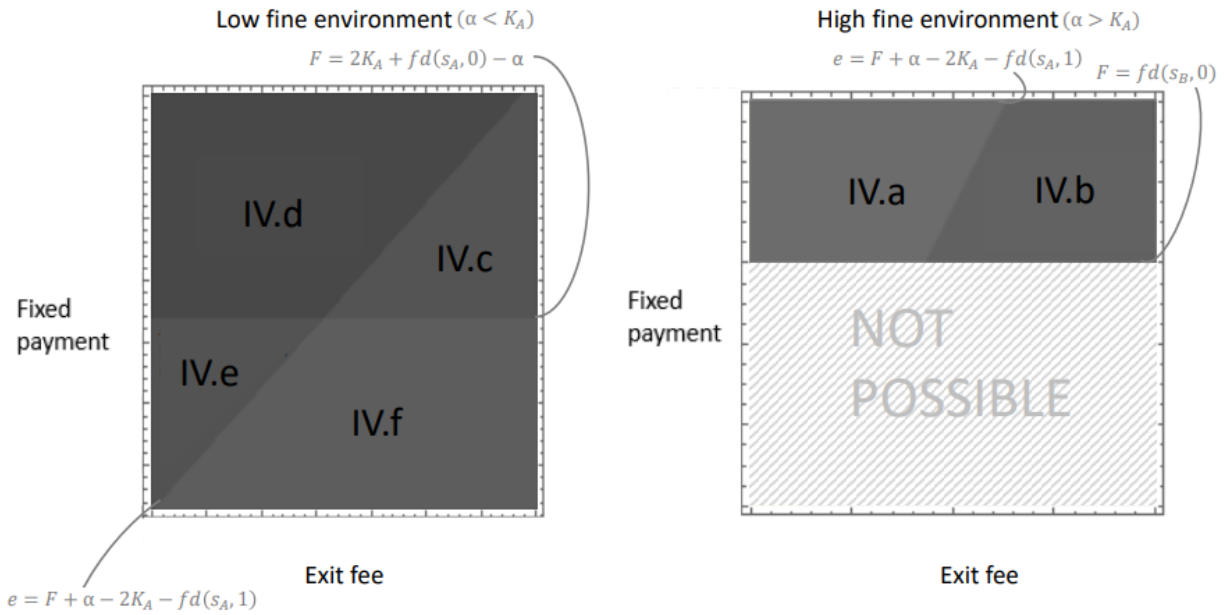

Figure 4.A.2 Six cases for the CRO based on the values of α, F and e under a good outside option and moderate exit fee.

(IV.a) When $F > fd(s_B, 0)$, $F + \alpha - 2K_A - fd(s_A, 0) > fd(s_B, 0) + \alpha - 2K_A - fd(s_A, 0) = 2(\alpha - K_A)$. Then, when $\alpha > K_A$, $F + \alpha - 2K_A - fd(s_A, 0) > 0$. If, in addition, $e < F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys an "A" team if $c = 0$ by Proposition 2(ii), if $c = 1$ and $j = W$ by Proposition 2(i), and if $c = 1$ and $j = S$ by Proposition 2(ii). By Lemma 1, $\Pi^P_{i,j}\big(d_i(s_A, 1)\big) > \Pi^P_{i,j}\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company commit to the CRO (Eq. 11).

(IV.b) When $\alpha > K_A$ and $e > F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys an "A" team if $c = 0$ by Proposition 2(ii) (as $F + \alpha - 2K_A - fd(s_A, 0) > 0$), and if $c = 1$ and $j = W$ by Proposition 2(i) but deploys a "B" team if $c = 1$ and $j = S$ by Proposition 2(ii). By Lemma 1, $\Pi^P_{i,W}\big(d_i(s_A, 1)\big) > \Pi^P_{i,W}\big(d_i(s_A, 0)\big)$ and the weak type commits to the CRO. Since $d(s_A, 0) < d_o$ and $d_o < d(s_B, 1)$, it must be that $w < s_A - s_B$ (i.e., the effectiveness of commitment is less than the marginal effectiveness of the "A" team). Since $d_i(s_B, 1) > d_i(s_A, 0)$ and by Lemma 1, $\Pi^P_{1,S}\big(d_1(s_B, 1)\big) < \Pi^P_{1,S}\big(d_1(s_A, 0)\big)$. As $d(s_A, 0) < d_o$ and by Lemma 1, $\Pi^P_{2,S}(d_o) < \Pi^P_{2,S}\big(d_2(s_A, 0)\big)$. Thus, the strong type does not commit to the CRO (Eq. 12).

(IV.c) When $\alpha < K_A$, $F > 2K_A + fd(s_A, 0) - \alpha$ and $e > F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys an "A" team if $c = 0$ by Proposition 2(ii), but deploys a "B" team if $c = 1$ and $j = W$ by Proposition 2(i), and if $c = 1$ and $j = S$ by Proposition 2(ii). Since $d(s_A, 0) < d_o$ and $d_o < d(s_B, 1)$, it must be that $w < s_A - s_B$. Since $d_i(s_B, 1) > d_i(s_A, 0)$ and by Lemma 1, $\Pi^P_{i,W}\big(d_i(s_B, 1)\big) < \Pi^P_{i,W}\big(d_i(s_A, 0)\big)$. Thus, the weak type does not commit. Similarly, $\Pi^P_{1,S}\big(d_1(s_B, 1)\big) < \Pi^P_{1,S}\big(d_1(s_A, 0)\big)$ and since $d(s_A, 0) < d_o$ and by Lemma 1, $\Pi^P_{2,S}(d_o) < \Pi^P_{2,S}\big(d_2(s_A, 0)\big)$. Thus, the strong type also does not commit to the CRO (Eq. 13).

(IV.d) When $\alpha < K_A$, $F > 2K_A + fd(s_A, 0) - \alpha$ and $e < F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys an "A" team if $c = 0$ by Proposition 2(ii), if $c = 1$ and $j = S$ by Proposition 2(ii) but deploys a "B" team if $c = 1$ and $j = W$ by Proposition 2(i). Since $d(s_A, 0) < d_o$ and $d_o < d(s_B, 1)$, it must be that $w < s_A - s_B$. Since $d_i(s_B, 1) > d_i(s_A, 0)$ and by Lemma 1, $\Pi^P_{i,W}\big(d_i(s_B, 1)\big) < \Pi^P_{i,W}\big(d_i(s_A, 0)\big)$. Thus, the weak type does not commit to the CRO. By Lemma 1, $\Pi^P_{i,S}\big(d_i(s_A, 1)\big) > \Pi^P_{i,S}\big(d_i(s_A, 0)\big)$. Thus, the strong type commits to the CRO (Eq. 14).

(IV.e) When $\alpha < \mathrm{K_A}$, $F < 2K_A + fd(s_A, 0) - \alpha$ and $e < F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys a "B" team if $c = 0$ by Proposition 2(ii), and if $c = 1$ and $j = W$ by Proposition 2(i), but deploys an "A" team if $c = 1$ and $j = S$ by Proposition 2(ii). Recall $w > 0$ and $s_A > s_B$. Then, $d_1(s_A, 1) < d_1(s_B, 0)$ and by Lemma 1, $\Pi^P_{1,S}\big(d_1(s_A, 1)\big) > \Pi^P_{1,S}\big(d_1(s_B, 0)\big)$. Since $d(s_A, 0) < d_o$, by Lemma 1, $\Pi^P_{2,S}\big(d_2(s_A, 1)\big) > \Pi^P_{2,S}(d_o)$. Thus, the strong type commits to the CRO.

For the weak type, using arguments similar to the ones in the proof of Case III, we can show that

- if $w > d_2(s_B, 1) - d_o$, the gain from the first period for the weak type exceeds the loss from not going with outside option in second period. Thus, the weak type commits to the CRO (Eq. 15).
- if $w < d_2(s_B, 1) - d_o$, the gain from the first period for the weak type is less than the loss from not going with outside option in second period. Thus, the weak type does not commit to the CRO (Eq. 16).

(IV.f) When $\alpha < K_A$, $F < 2K_A + fd(s_A, 0) - \alpha$ and $e > F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys a "B" team if $c = 0$ by Proposition 2(ii), if $c = 1$ and $j = W$ by Proposition 2(i), and if $c = 1$ and $j = S$ by Proposition 2(ii).

- The gain from commitment in the first period is $\Pi^P_{1,j}\big(d_1(s_B, 1)\big) - \Pi^P_{1,j}\big(d_1(s_B, 0)\big) = \big(m_j l - f\big)w$. The cost of commitment for the strong type in the second period is e. If $(m_S l - f)w > e$, the gain exceeds the exit fee and thus the strong commits to the CRO. The loss for the weak type from not going with outside option in the second period is $\Pi^P_{2,W}(d_o) - \Pi^P_{2,W}\big(d_2(s_B, 1)\big) = (m_W l - f)(d(s_B, 1) - d_o)$. If $w > d_2(s_B, 1) - d_o$, the gain from the first period exceeds the loss. Thus, the weak type also commits to the CRO (Eq. 17).

- If instead $w < d_2(s_B, 1) - d_o$ and $(m_S l - f)w > e$, the gain in the first period is less than the loss in second period. Thus, the weak type does not commit to the CRO (Eq. 18).

- If $w < d_2(s_B, 1) - d_o$ and $w(m_S l - f) < e$, the gain from commitment for the strong type in the first period is less than the exit fee. Thus, the strong type also does not commit to the CRO (Eq. 19).

Case V. Good outside option & low exit fees: When $d_o < d(s_B, 1) < d(s_B, 0)$ and $e < \phi_W \delta < \phi_S \delta$, the pharma company does not rehire (breaks its commitment to) a "B" team if $c = 0$ ($c = 1$) by Proposition 1(b). As illustrated in Figure 4.A.3, there are four cases for the CRO based on the values of α, F, and e:

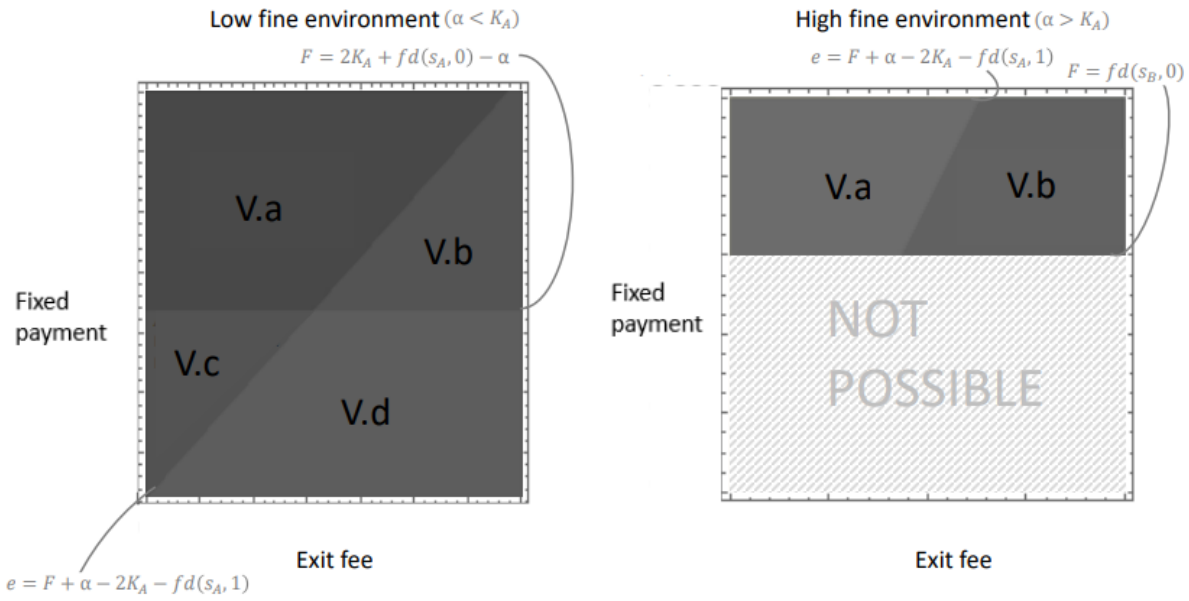

Figure 4.A.1: Four cases for the CRO based on the values of α, F and e under a good outside option and low exit fee.

(V.a) When $F > \max\{2K_A + fd(s_A, 0) - \alpha, fd(s_B, 0)\}$ and $e < F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys an "A" team if $c = 0$ or $c = 1$ by Proposition 2(ii). By Lemma 1, $\Pi^P_{i,j}\big(d_i(s_A, 1)\big) > \Pi^P_{i,j}\big(d_i(s_A, 0)\big)$. Thus, both types of pharma company commit to the CRO (Eq. 20).

(V.b) When $F > \max\{2K_A + fd(s_A, 0) - \alpha, fd(s_B, 0)\}$ and $e > F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys an "A" team ("B" team) if $c = 0$ ($c = 1$) by Proposition 2(ii). Since $d(s_A, 0) < d_o$ and $d_o < d(s_B, 1)$, it must be that $w < s_A - s_B$. As $d_i(s_B, 1) > d_i(s_A, 0)$ and by Lemma 1, $\Pi^P_{1,j}\big(d_1(s_B, 1)\big) < \Pi^P_{1,j}\big(d_1(s_A, 0)\big)$. As $d(s_A, 0) < d_o$ and by Lemma 1, $\Pi^P_{2,j}(d_o) < \Pi^P_{2,j}\big(d_2(s_A, 0)\big)$. Thus, both types of pharma company do not commit to the CRO (Eq. 21).

(V.c) When $\alpha < K_A$, $F < 2K_A + fd(s_A, 0) - \alpha$ and $e < F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys a "B" team ("A" team) if $c = 0$ ($c = 1$) by Proposition 2(ii). Since $w + s_A > s_B$, $d_1(s_A, 1) < d_1(s_B, 0)$ and by Lemma 1, $\Pi^P_{1,j}\big(d_1(s_A, 1)\big) > \Pi^P_{1,j}\big(d_1(s_B, 0)\big)$. Since $d(s_A, 0) < d_o$ and by Lemma 1, $\Pi^P_{2,j}\big(d_2(s_A, 1)\big) > \Pi^P_{2,j}(d_o)$. Thus, both types commit to the CRO (Eq. 22).

(V.d) When $\alpha < K_A$, $F < 2K_A + fd(s_A, 0) - \alpha$ and $e > F + \alpha - 2K_A - fd(s_A, 1)$, the CRO deploys a "B" team if $c = 0$ or $c = 1$ by Proposition 2(ii). Using arguments similar to the ones in the proof of Case III, we can show that

- if $w(m_W l - f) > e$, the gain from commitment in the first period exceeds the exit fee and both types commit to the CRO (Eq. 23).

- if $w(m_W l - f) < e < w(m_S l - f)$, the gain from commitment exceeds the exit fee only for the strong type and thus only the strong type commits to the CRO (Eq. 24).

- if $w(m_S l - f) < e$, the gain from commitment in the first period is less than the exit fee and both types do not commit to the CRO (Eq. 25). ■

Proof of Theorem 2: Theorem 2 states that in the environments characterized by Eq. 22 for both pharma company types and Eq. 15, 16 for the strong type (Theorem 1) result in (i) the highest reduction in duration, reducing the duration of both projects ($d_1(s_A, 1) < d_1(s_B, 0)$ and $d_2(s_A, 1) < d_o$, (ii) the largest total gain in payoffs for the pharma company, and (iii) a higher payoff for the CRO.

(i) We first group the SPNE of Table 4.3 when commitment is preferred into 6 cases as displayed in Table 4.A.1. The grouping puts together cases with the same outcome and players' best responses.

To prove the result regarding the greatest duration reduction, we evaluate and compare the total reduction in duration for each case where commitment is preferred to no commitment (Table 4.A.1). Consider Case 1. In these equilibria, the choice to offer commitment results in a reduction of $d_i(s_A, 0) - d_i(s_A, 1) = (\tau - s_A) - (\tau - s_A - w) = w$ for project i, resulting in a total reduction of $2w$. In the same manner, the total reduction in duration can be evaluated for Cases 2–6.

Table 4.A.1: Durations when commitment is preferred.

Case	Equilibria	Project durations when			Total reduction in duration through commitment
		$c = 1$:	vs.	$c = 0$:	
1	1,3,7,11,20 (both) & 12 (weak) & 14 (strong)	$d_1(s_A, 1) + d_2(s_A, 1)$		$d_1(s_A, 0) + d_2(s_A, 0)$	$2w$
2	22 (both) &15,16 (strong)	$d_1(s_A, 1) + d_2(s_A, 1)$		$d_1(s_B, 0) + d_o$	$2w - \tau + d_o + 2s_A - s_B$
3	2 (both)	$d_1(s_B, 1) + d_2(s_B, 1)$		$d_1(s_B, 0) + d_2(s_B, 0)$	$2w$
4	5 (both)	$d_1(s_B, 1) + d_2(s_B, 1)$		$d_1(s_A, 0) + d_2(s_A, 0)$	$2w - 2s_A + 2s_B$
5	4,8 (both) & 15,17 (weak)	$d_1(s_B, 1) + d_2(s_B, 1)$		$d_1(s_B, 0) + d_o$	$2w - \tau + d_o + s_B$
6	23 (both) & 17,18,24 (strong)	$d_1(s_B, 1) + d_o$		$d_1(s_B, 0) + d_o$	w

It is easy to show that the total reduction in duration in Case 2 is the greatest. The expression in Table 4.A.1 for Case 2 can be re–written as $2w - \tau + d_o + s_A + (s_A - s_B)$. Given $w > 0$, $\tau - s_A < d_o$ (Lemma 1) and $s_A > s_B$, $2w > 0$, $-\tau + d_o + s_A > 0$ and $s_A - s_B > 0$. It is clear to see that Case 2 results in a higher duration reduction than Cases 1, 3 and 6. Since $-2s_A + 2s_B < 0$, Case 4 results in a smaller total reduction in duration than Case 2. Comparing Case 2 to Case 5, we see that $2s_A - s_B > s_B$ since $s_A > s_B$ meaning $2w - \tau + d_o + 2s_A - s_B > 2w - \tau + d_o + s_B$.

(ii) Table 4.A.2 uses the same grouping as Table 4.A.1 but compares the pharma company's payoffs rather than project duration.

To prove the result regarding the largest gain in payoffs for the pharma company, we evaluate and compare the total gain in payoffs for each outcome where commitment is preferred to no commitment (Table 4.A.2). Again, consider Case 1. The choice to offer commitment results in a gain of

$$\begin{aligned}\Pi^P_{i,j}(s_A, c) - \Pi^P_{i,j}(s_A) &= \left[m_j\left(1 - l d_i(s_A, c)\right) - \left(F - f d_i(s_A, c)\right)\right] \\ &\quad - \left[m_j\left(1 - l d_i(s_A)\right) - \left(F - f d_i(s_A)\right)\right] \\ = \; -w(f - m_j l)\end{aligned}$$

for project i, resulting in a total gain of $-2w\left(f - m_j l\right)$. In the same manner, the total gain in payoffs can be evaluated for Cases 2–6.

Table 4.A.2: Pharmaceutical company payoff when commitment is preferred.

Case	Equilibria	Pharmaceutical company's payoff when $c=1$:	vs.	$c=0$:	Total gain in payoff through commitment
1	1,3,7,11,20 (both) & 12 (weak) & 14 (strong)	$\Pi^{P}_{1,j}(d(s_A,1))+\Pi^{P}_{2,j}(d(s_A,1))$		$\Pi^{P}_{1,j}(d(s_A,0))+\Pi^{P}_{2,j}(d(s_A,0))$	$-2w(f-m_jl)$
2	22 (both) & 15,16 (strong)	$\Pi^{P}_{1,j}(d(s_A,1))+\Pi^{P}_{2,j}(d(s_A,1))$		$\Pi^{P}_{1,j}(d(s_B,0))+\Pi^{P}_{2,j}(d_o)$	$-((f-m_jl)(2w-\tau+d_o+2s_A-s_B))$
3	2 (both)	$\Pi^{P}_{1,j}(d(s_B,1))+\Pi^{P}_{2,j}(d(s_B,1))$		$\Pi^{P}_{1,j}(d(s_B,0))+\Pi^{P}_{2,j}(d(s_B,0))$	$-2w(f-m_jl)$
4	5 (both)	$\Pi^{P}_{1,j}(d(s_B,1))+\Pi^{P}_{2,j}(d(s_B,1))$		$\Pi^{P}_{1,j}(d(s_A,0))+\Pi^{P}_{2,j}(d(s_A,0))$	$-2(f-m_jl)(w-s_A+s_B)$
5	4,8 (both) & 15,17 (weak)	$\Pi^{P}_{1,j}(d(s_B,1))+\Pi^{P}_{2,j}(d(s_B,1))$		$\Pi^{P}_{1,j}(d(s_B,0))+\Pi^{P}_{2,j}(d_o)$	$-((f-m_jl)(2w-\tau+d_o+s_B))$
6	23 (both) & 17,18,24 (strong)	$\Pi^{P}_{1,j}(d(s_B,1))+\Pi^{P}_{2,j}(d_o)$		$\Pi^{P}_{1,j}(d(s_B,0))+\Pi^{P}_{2,j}(d_o)$	$-e-w(f-m_jl)$

We can demonstrate that the pharma company makes the largest total gain in Case 2 equilibria. By Lemma 1, $f < m_j l$. Consistent with the rationale for the highest duration reduction (above), it follows that the gain in Case 2 is greater than that of Case 1 and Case 3 if $\tau < d_o + 2s_A - s_B$. This holds since $\tau - s_A < d_o$ and $s_A > s_B$. Since $-2s_A + 2s_B < 0$, Case 4 results in a smaller total gain than Case 2. Case 5 also results in a smaller total gain than Case 2 since $s_A > s_B$ (meaning $2s_A - s_B > s_B$). Finally, Case 6 results in a larger gain than Case 2 $(-e - w(f - m_j l) > \big((f - m_j l)(2w - \tau + d_o + 2s_A - s_B)\big))$ when $e < (f - m_j l)(w - \tau + d_o + 2s_A - S_B)$. However, since $f - m_j l < 0$ and $e > 0$, the expression $2w - \tau + d_o + 2s_A - s_B$ must be positive. This cannot hold since $\tau - s_A - w < d_o$ (Lemma 1). Therefore, $e > (f - m_j l)(w - \tau + d_o + 2s_A - S_B)$ and Case 2 results in a larger gain than Case 6.

(iii) To prove the result regarding a higher payoff for the CRO under commitment for the environment characterized by Eq. 22 for both pharma company types and Eq. 15, 16 for the strong type, we compare the total CRO payoff under $c = 1$ $(\Pi_1^C(d_1(s_A, 1) + \Pi_2^C(d_2(s_A, 1))$ and total CRO payoff under $c = 0$ $(\Pi_1^C(S_B, 0))$. It is easy to show that $\Pi_1^C(d_1(s_A, 1) + \Pi_2^C(d_2(s_A, 1) < \Pi_1^C(S_B, 0)$ cannot hold. The expression reduces to $F < 2K_A - 2fw + f\tau - 2fs_A + fs_B$. However, the aforementioned equilibria only occur when $e < F - 2K_A + fw - f\tau + 2fs_A - fs_B$. Since $e > 0$, $F > 2K_A - 2fw + f\tau - 2fs_A + fs_B$. ■

Proof of Proposition 3: When $d_o < d(s_B, 1)$ and $\phi_W \delta < e < \phi_S \delta$, the weak type pharma company's best response in the third stage is to honor its commitment to the "B" team when $c = 1$, while the strong type pharma company's is to break it. If the CRO deploys its "A" team, then both types of pharma company will choose to continue the strategic partnership.

If the CRO deploys its "A" team, the CRO earns a payoff of

$$\boldsymbol{A} = \Pi_1^C\big(d_1(s_A, 1)\big) + \Pi_2^C\big(d_2(s_A, 1)\big) = 2F - 2f(\tau - s_A - \omega) - 2K_A.$$

Instead, if the CRO deploys its "B" team, it earns a payoff of

$$\boldsymbol{B_S} = \Pi_1^C\big(d_1(s_B, 1)\big) + e = F - f(\tau - s_B - \omega) + e,$$

with a chance of b and a payoff of

$$\boldsymbol{B_W} = \Pi_1^C\big(d_1(s_B, 1)\big) + \Pi_2^C\big(d_2(s_B, 1)\big) = 2F - 2\,f(\tau - s_B - \omega)),$$

with a chance of $1 - b$.

Let $\Pi_{\mathrm{A}}^{\mathrm{C}} = \mathbf{A}$ and $\Pi_B^C = b\boldsymbol{B_S} + (1 - b)\boldsymbol{B_W}$. Then,

$$\Pi_A^C - \Pi_B^C = \boldsymbol{A} - b\boldsymbol{B_S} - (1 - b)\boldsymbol{B_W} = b(\boldsymbol{A} - \boldsymbol{B_S}) + (1 - b)(\boldsymbol{A} - \boldsymbol{B_W})$$

Let $\bar{b}$ be the b value for which $\Pi_A^C - \Pi_B^C = 0$:

$$\bar{b} = \frac{\boldsymbol{B_W} - \boldsymbol{A}}{\boldsymbol{B_W} - \boldsymbol{B_S}} = \frac{\Pi_1^C\big(d_1(s_B, 1)\big) + \Pi_2^C\big(d_2(s_B, 1)\big) - \Pi_1^C\big(d_1(s_A, 1)\big) + \Pi_2^C\big(d_2(s_A, 1)\big)}{\Pi_2^C\big(d_2(s_B, 1)\big) - e}$$

Recall $\alpha = f(s_A - s_B)$. Note that $\boldsymbol{A} - \boldsymbol{B_W} = 2\alpha - 2K_A$ and $\boldsymbol{A} - \boldsymbol{B_S} = F + \alpha - fd(s_A, 1) - 2K_A - e$. If $\alpha > K_A$, $\boldsymbol{A} > \boldsymbol{B_W}$ and if $\alpha < K_A$, $\boldsymbol{A} < \boldsymbol{B_W}$. Similarly, if $F + \alpha - 2K_A - fd(s_A, 1) > e$, $\boldsymbol{A} > \boldsymbol{B_S}$ and if $F + \alpha - 2K_A - fd(s_A, 1) < e$, $\boldsymbol{A} < \boldsymbol{B_S}$.Using these relations, the table below compares the CRO's payoffs with an "A" vs. "B" team deployment.

	$F+\alpha-2K_A-fd(s_A,1)>e$ (Low exit fee environment)	$F+\alpha-2K_A-fd(s_A,1)<e$ (High exit fee environment)
$\alpha > K_A$ (High fine)	$\mathbf{A} > \mathbf{B_W}$ and $\mathbf{A} > \mathbf{B_S}$ $\Pi_A^C > \Pi_B^C$, $0 \le b \le 1$	$\mathbf{A} > \mathbf{B_W}$ and $\mathbf{A} < \mathbf{B_S}$ $\Pi_A^C > \Pi_B^C$, $0 \le b \le \bar{b}$ $\Pi_A^C < \Pi_B^C$, $\bar{b} \le b \le 1$
$\alpha < K_A$ (Low fine)	$\mathbf{A} < \mathbf{B_W}$ and $\mathbf{A} > \mathbf{B_S}$ $\Pi_A^C > \Pi_B^C$, $\bar{b} \le b \le 1$ $\Pi_A^C < \Pi_B^C$, $0 \le b \le \bar{b}$	$\mathbf{A} < \mathbf{B_W}$ and $\mathbf{A} < \mathbf{B_S}$ $\Pi_A^C < \Pi_B^C$, $0 \le b \le 1$

The CRO deploys an "A" team when $\Pi_A^C > \Pi_B^C$, and deploys a "B" team when $\Pi_A^C < \Pi_B^C$. ■

Proof of Theorem 3: Recall, in comparing the full information and asymmetric information model, we limit our discussion to four environments (characterized by Eq. 12, 14–16 in Table 4.3); the environments in which transparency results in different outcomes and payoffs for the CRO and pharma company. In this theorem, we consider the settings − low fine ($\alpha < K_A$) and low exit fee ($e + fd(s_A, 1) < F + \alpha - 2K_A$) − under which Eq. 14–16 are the SPNE.

When $d_o < d(s_B, 1) < d(s_B, 0)$ and $\phi_W \delta < e < \phi_S \delta$, both types of pharma company do not rehire a "B" team if $c = 0$ by Proposition 1(b), the weak type keeps its commitment to the "B" team if $c = 1$ by Proposition 1(a), and the strong type breaks its commitment to the "B" team if $c = 1$ by Proposition 1(b). That is, the strong type and weak type differ in their third stage actions under commitment. Consider three environments further characterized by a low fine ($\alpha < K_A$), low exit fee ($e + fd(s_A, 1) < F + \alpha - 2K_A$), and

- a high fixed payment ($fd(s_A, 0) < F + \alpha - 2K_A$) (Environment 1),
- a low fixed payment ($F + \alpha - 2K_A < fd(s_A, 0)$) and a high effectiveness of commitment ($w > d_2(s_B, 1) - d_o$\$) (Environment 2), and
- a low fixed payment ($F + \alpha - 2K_A < fd(s_A, 0)$) and low effectiveness of commitment ($w < d_2(s_B, 1) - d_o$) (Environment 3).

Environment 1: We know that in all three environments the weak (strong) type keeps (breaks) its commitment to the "B" team if $c = 1$ and both types will not rehire a "B" team if $c = 0$. To find

the PBE, we consider the CRO's best response in this environment. Under a high fixed payment, the CRO deploys an "A" team when $c = 0$ by Proposition 2(ii). There are two cases for the CRO when $c = 1$:

- If $0 < b \leq \bar{b}$, the CRO deploys a "B" team (Proposition 3). Since $d(s_A, 0) < d_o$ and $d_o < d(s_B, 1)$, $w < s_A - s_B$. Since $d_i(s_B, 1) > d_i(s_A, 0)$ and by Lemma 1, the weak (strong) type does not commit to the CRO as $\Pi^P_{i,W}\big(d_i(s_B, 1)\big) > \Pi^P_{i,W}\big(d_i(s_A, 0)\big)$ $(\Pi^P_{1,S}\big(d_1(s_B, 1)\big) + \Pi^P_{2,S}(d_o) < \Pi^P_{1,S}\big(d_1(s_A, 0)\big) + \Pi^P_{2,S}\big(d_2(s_A, 0)\big))$.
- If $\bar{b} < b \leq 1$, the CRO deploys an "A" team (Proposition 3). By Lemma 1, both types of pharma company commit to the CRO since $\Pi^P_{i,j}\big(d_i(s_A, 1)\big) > \Pi^P_{i,j}\big(d_i(s_A, 0)\big)$.

Table 4.A.3 Comparison of the SPNE and PBE in Environment 1.

		PBE	
	SPNE (Theorem 1: Eq. 14)	$0 < b \leq \bar{b}$	$\bar{b} < b \leq 1$
Stage 1:	Weak: TR Strong: SP	Weak: TR Strong: TR	Weak: SP Strong: SP
Stage 2:	"A" if TR and $j = W$ "A" if SP and $j = S$	"A" if TR	"A" if SP
Stage 3:	Weak: Rehire "A" Strong: Maintain "A"	Weak: Rehire "A" Strong: Rehire "A"	Weak: Maintain "A" Strong: Maintain "A"
Pharma payoff:	Weak: $\Pi^P_{1,W}(d_1(s_A, 0)) + \Pi^P_{2,W}(d_2(s_A, 0))$ Strong: $\Pi^P_{1,S}(d_1(s_A, 1)) + \Pi^P_{2,S}(d_2(s_A, 1))$	Weak: $\Pi^P_{1,W}(d_1(s_A, 0)) + \Pi^P_{2,W}(d_2(s_A, 0))$ Strong: $\Pi^P_{1,S}(d_1(s_A, 0)) + \Pi^P_{2,S}(d_2(s_A, 0))$	Weak: $\Pi^P_{1,W}(d_1(s_A, 1)) + \Pi^P_{2,W}(d_2(s_A, 1))$ Strong: $\Pi^P_{1,S}(d_1(s_A, 1)) + \Pi^P_{2,S}(d_2(s_A, 1))$

Comparing the pharma's payoffs under full information and asymmetric information (Table 4.A.3):

- when $0 < b \leq \bar{b}$, the weak type is no better off offering transparency to the CRO whereas the strong type is better off (by Lemma 1).
- when $\bar{b} < b \leq 1$, weak type is worse off offering transparency to the CRO (by Lemma 1) whereas the strong type is no worse off.

Environment 2: Under a low fixed payment, the CRO deploys a "B" team when $c = 0$ by Proposition 2(ii). There are two cases for the CRO when $c = 1$:

- If $0 < b \leq \bar{b}$, the CRO deploys a "B" team (Proposition 3). Recall $\delta = d(s_B, 1) - d_o$ and $\phi_S = m_S l - f$. Since $e < \phi_S \delta$ and $w > \delta$, $e < w\phi_S$. Thus, the strong type commits to the CRO since $\Pi^P_{1,S}\big(d_1(s_B, 1)\big) + \Pi^P_{2,S}(d_o) > \Pi^P_{1,S}\big(d_1(s_B, 0)\big) + \Pi^P_{2,S}(d_o)$. Since $w > \delta$, i.e.,

under a high effectiveness of commitment, the weak type also commits to the CRO as $\Pi^P_{1,W}\big(d_1(s_B,1)\big)+\Pi^P_{2,W}\big(d_2(s_B,1)\big) > \Pi^P_{1,W}\big(d_1(s_B,0)\big)+\Pi^P_{2,W}(d_o)$.

- If $\bar{b} < b \leq 1$, the CRO deploys an "A" team (Proposition 3). Since $w + s_A > s_B$, $d_1(s_A,1) < d_1(s_B,0)$. In addition, since $d_i(s_A,0) < d_o$ and by Lemma 1, both types commit to the CRO as $\Pi^P_{1,j}\big(d_1(s_A,1)\big) > \Pi^P_{1,j}\big(d_1(s_B,0)\big)$ and $\Pi^P_{2,j}\big(d_2(s_A,1)\big) > \Pi^P_{2,j}\big(d_1(s_B,0)\big)$.

Table 4.A.4 Comparison of the SPNE and PBE in Environment 2.

		PBE	
	SPNE (Theorem 1: Eq. 15)	$0 < b \leq \bar{b}$	$\bar{b} < b \leq 1$
Stage 1:	Weak: SP Strong: SP	Weak: SP Strong: SP	Weak: SP Strong: SP
Stage 2:	"B" if SP and $j = W$ "A" if SP and $j = S$	"B" if SP	"A" if SP
Stage 3:	Weak: Maintain "B" Strong: Maintain "A"	Weak: Maintain "B" Strong: Terminate "B"	Weak: Maintain "A" Strong: Maintain "A"
Pharma payoff:	Weak: $\Pi^P_{1,W}(d_1(s_B,1))+\Pi^P_{2,W}(d_2(s_B,1))$ Strong: $\Pi^P_{1,S}(d_1(s_A,1))+\Pi^P_{2,S}(d_2(s_A,1))$	Weak: $\Pi^P_{1,W}(d_1(s_B,1))+\Pi^P_{2,W}(d_2(s_B,1))$ Strong: $\Pi^P_{1,S}(d_1(s_B,1))+\Pi^P_{2,S}(d_o)$	Weak: $\Pi^P_{1,W}(d_1(s_A,1))+\Pi^P_{2,W}(d_2(s_A,1))$ Strong: $\Pi^P_{1,S}(d_1(s_A,1))+\Pi^P_{2,S}(d_2(s_A,1))$

Recall $s_A > s_B$ and $d(s_A,0) < d_o$. Comparing the pharma company's payoff under full information to its payoff under asymmetric information (Table 4.A.4):

- when $0 < b \leq \bar{b}$, the weak type is no better off offering transparency to the CRO whereas the strong type is better off (by Lemma 1).
- when $\bar{b} < b \leq 1$, weak type is worse off offering transparency to the CRO (by Lemma 1) whereas the strong type is no worse off.

Environment 3: Again, under low a low fixed payment, the CRO deploys a "B" team when $c = 0$ by Proposition 2(ii). There are two cases for the CRO when $c = 1$:

- If $0 < b \leq \bar{b}$, the CRO deploys a "B" team (Proposition 3). Recall $\delta = d(s_B,1) - d_o$ and $\phi_S = m_S l - f$. Since $e < \phi_S\delta$ and $w < \delta$, $e > w\phi_S$. Thus, the strong type does not commit to the CRO since $\Pi^P_{1,S}\big(d_1(s_B,1)\big)+\Pi^P_{2,S}(d_o) < \Pi^P_{1,S}\big(d_1(s_B,0)\big)+\Pi^P_{2,S}(d_o)$. Since $w < \delta$, i.e., under a low effectiveness of commitment, the weak type also does not commit to the CRO as $\Pi^P_{1,W}\big(d_1(s_B,1)\big)+\Pi^P_{2,W}\big(d_2(s_B,1)\big) < \Pi^P_{1,W}\big(d_1(s_B,0)\big)+\Pi^P_{2,W}(d_o)$.
- If $\bar{b} < b \leq 1$, the CRO deploys an "A" team (Proposition 3). Since $w + s_A > s_B$, $d_1(s_A,1) < d_1(s_B,0)$. In addition, since $d_i(s_A,0) < d_o$ and by Lemma 1, both types commit to the CRO since $\Pi^P_{1,j}\big(d_1(s_A,1)\big) > \Pi^P_{1,j}\big(d_1(s_B,0)\big)$ and $\Pi^P_{2,j}\big(d_2(s_A,1)\big) > \Pi^P_{2,j}(d_o)$.

Table 4.A.5 Comparison of the SPNE and PBE in Environment 3.

		PBE	
	SPNE (Theorem 1: Eq. 16)	$0 < b \leq \bar{b}$	$\bar{b} < b \leq 1$
Stage 1:	Weak: TR Strong: SP	Weak: TR Strong: TR	Weak: SP Strong: SP
Stage 2:	"B" if TR and $j = W$ "A" if SP and $j = S$	"B" if TR	"A" if SP
Stage 3:	Weak: Fire "B" Strong: Maintain "A"	Weak: Fire "B" Strong: Fire "B"	Weak: Maintain "A" Strong: Maintain "A"
Pharma payoff:	Weak: $\Pi^P_{1,W}(d_1(s_B,0)) + \Pi^P_{2,W}(d_o)$ Strong: $\Pi^P_{1,S}(d_1(s_A,1)) + \Pi^P_{2,S}(d_2(s_A,1))$	Weak: $\Pi^P_{1,W}(d_1(s_B,0)) + \Pi^P_{2,W}(d_o)$ Strong: $\Pi^P_{1,S}(d_1(s_B,0)) + \Pi^P_{2,S}(d_o)$	Weak: $\Pi^P_{1,W}(d_1(s_A,1)) + \Pi^P_{2,W}(d_2(s_A,1))$ Strong: $\Pi^P_{1,S}(d_1(s_A,1)) + \Pi^P_{2,S}(d_2(s_A,1))$

Recall $d(s_A, 0) < d_o$ and $s_A > s_B$. Comparing the pharma company's payoff under full information to its payoff under asymmetric information (Table 4.A.5):

- when $0 < b \leq \bar{b}$, the weak type is no better off offering transparency to the CRO whereas the strong type is better off (by Lemma 1).
- when $\bar{b} < b \leq 1$, weak type is worse off offering transparency to the CRO (by Lemma 1) whereas the strong type is no worse off.

Combining the results in the three environments, we prove the theorem. ■

Proof of Theorem 4: As mentioned in the proof of Theorem 3, in comparing the full information and asymmetric information model, we limit our discussion to four environments (characterized by Eq. 12, 14–16 in Table 4.3); the final of which (Eq. 12) will now be discussed.

When $d_o < d(s_B, 1) < d(s_B, 0)$ and $\phi_W \delta < e < \phi_S \delta$, both types of pharma company do not rehire a "B" team if $c = 0$ by Proposition 1(b), the weak type keeps its commitment to the "B" team if $c = 1$ by Proposition 1(a), and the strong type breaks its commitment to the "B" team if $c = 1$ by Proposition 1(b). That is, the weak type and strong type differ in their third stage actions under commitment. Consider the environment further characterized by a high fine ($\alpha > K_A$) and a high exit fee ($e > f + \alpha - 2K_A - fd(s_A, 1)$).

To find the PBE, we consider the CRO's best response in this environment. Under a high fixed payment, the CRO deploys an "A" team if $c = 0$ by Proposition 1(b). There are two cases for the CRO when $c = 1$:

- If $0 < b \leq \bar{b}$, the CRO deploys an "A" team (Proposition 3). By Lemma 1, both types commit to the CRO since $\Pi^P_{i,j}(d_i(s_A, 1)) > \Pi^P_{i,j}(d_i(s_A, 0)$.
- If $\bar{b} < b \leq 1$, the CRO deploys a "B" team (Proposition 3). Since $d(s_A, 0) < d_o$ and $d_o < d(s_B, 1), w < s_A - s_B$. Thus, the weak type does not commit to the CRO as $\Pi^P_{i,W}\big(d_i(s_B, 1)\big) < \Pi^P_{i,W}\big(d_i(s_A, 0)\big)$ and the strong type also does not commit to the CRO as $\Pi^P_{1,S}\big(d_1(s_B, 1)\big) < \Pi^P_{1,S}\big(d_1(s_A, 0)\big)$ and $\Pi^P_{2,S}(d_o) < \Pi^P_{2,S}\big(d_2(s_A, 0)\big)$.

Table 4.A.6 Comparison of the SPNE and PBE.

		PBE	
	SPNE (Theorem 1: Eq. 12)	$0 < b \leq \bar{b}$	$\bar{b} < b \leq 1$
Stage 1:	Weak: SP Strong: TR	Weak: SP Strong: SP	Weak: TR Strong: TR
Stage 2:	"A" if SP and $j = W$ "A" if TR and $j = S$	"A" if SP	"A" if TR
Stage 3:	Weak: Maintain "A" Strong: Rehire "A"	Weak: Maintain "A" Strong: Maintain "A"	Weak: Rehire "A" Strong: Rehire "A"
Pharma payoff:	Weak: $\Pi^P_{1,W}(d_1(s_A, 1)) + \Pi^P_{2,W}(d_2(s_A, 1))$ Strong: $\Pi^P_{1,S}(d_1(s_A, 0)) + \Pi^P_{2,S}(d_2(s_A, 0))$	Weak: $\Pi^P_{1,W}(d_1(s_A, 1)) + \Pi^P_{2,W}(d_2(s_A, 1))$ Strong: $\Pi^P_{1,S}(d_1(s_A, 1)) + \Pi^P_{2,S}(d_2(s_A, 1))$	Weak: $\Pi^P_{1,W}(d_1(s_A, 0)) + \Pi^P_{2,W}(d_2(s_A, 0))$ Strong: $\Pi^P_{1,S}(d_1(s_A, 0)) + \Pi^P_{2,S}(d_2(s_A, 0))$

The result in the theorem follows by comparing the pharma company's payoff under full information to its payoff under asymmetric information (Table 4.A.6):

- when $0 < b \leq \bar{b}$, the weak type is no better off offering transparency to the CRO whereas the strong type is worse off (by Lemma 1).
- when $\bar{b} < b \leq 1$, the weak type is better off offering transparency to the CRO (by Lemma 1) whereas the strong type is no worse off. ■

Chapter 5

Applying Systems Thinking to Inform Decentralized Clinical Trial Planning and Deployment

5.1 Introduction

There are many hurdles to overcome when identifying, enrolling, and retaining study participants in clinical research. These hurdles are associated with numerous factors, including patient access and willingness to participate; protocol demands and eligibility constraints; and physician willingness to refer and facilitate participation. Although 85% of people are willing to participate in clinical trials, for example, only a fraction do (CISCRP 2019). It has been estimated that less than 10% of eligible adult cancer patients participate in clinical trials (Unger et al. 2019). In a typical phase III clinical trial, more than one–third (37%) of clinical research sites under-enroll, and 11% fail to enroll even a single participant (Chaudhari et al. 2020). Moreover, due to dropout rates – on average estimated as high as 30% (Alexander 2013) – participant retention can compromise study results and carry significant financial consequences. In fact, the average cost per patient has risen by 70% in the past three years (Sonnenberg 2019). Further, recruitment and retention problems can delay clinical trial completion, costing sponsors up to $8 million daily (Hargreaves, 2016) in lost drug sales.

In conventional clinical trials, participants visit investigational sites, often located in large medical facilities in metropolitan areas. The centralization of operations in such locations far away from where potential participants live may hinder participation (Khozin and Coravos 2019). To illustrate, 70% of potential participants in the U.S. live more than 2 h away from the nearest study center (Anderson et al. 2018). A 2019 study assessing patient engagement in clinical trials with

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more than 12,000 respondents identified travel to and from sites as the top study participation burden, with 29% indicating that it was “somewhat” or “very burdensome” (Sine et al. 2021). In addition, these geographical constraints disproportionately affect underprivileged groups (e.g., people from lower socioeconomic groups may not be able to take time off work or afford to travel long distances for trial visits), particularly those with intersecting identities (e.g., racial minority women) (Goodson et al. 2022). This barrier may contribute to the lack of representation in clinical trials, jeopardizing external validity and generalizability of results and ultimately resulting in ineffective or even harmful drugs among certain demographic groups (Guerrero et al. 2018).

Clinical trial complexity has also grown significantly during the past decade, placing a substantial burden on investigative sites. Since 2010, for example, the average number of endpoints in phase II and III protocols has increased 27%, and the average number of procedures performed per patient visit has increased 22% (Getz et al. 2022, Medable 2020). However, this complexity has run counter to patient expectations of greater convenience of care (Sommer et al. 2018). Moreover, growing interest in real-world evidence (RWE) in clinical trial data generation has called for data collection from the point of routine care in addition to locations outside the brick-and-mortar boundaries of the healthcare system (Khozin and Coravos 2019).

The COVID-19 pandemic exposed the vulnerabilities of the conventional, site-centric clinical trial design in several ways (Medical Research Network 2020). First, the redirection of healthcare resources and staff to care for COVID-19 patients led to staff shortages, which were exacerbated by staff falling ill with COVID-19. Second, particularly early in the pandemic, on-site visits by clinical research associates were limited by the shift to a virtual setting due to government restrictions and regulatory guidance (Patil and Varner 2020). Access to sites was affected by geographical differences and the state of the pandemic. One survey of organizations within the sector showed that 35% up to 80% of sites were inaccessible (Colby and Breiten 2020). Third, travel restrictions and stay-at-home orders prevented participants from visiting sites for regular dosing and assessment. Some contracted COVID-19, while others skipped visits out of fear. According to a poll, in May 2020, nearly half of Americans (48%) said they missed or delayed receiving medical care due to the pandemic (Hamel et al. 2020), which was a key concern as missed visits and “out-of-window” visits lead to protocol deviations that jeopardized data integrity.

Finally, the pandemic also created shortages of ancillary supplies for clinical trials due to disruptions in the supply chain and logistical challenges involving transportation caused by lockdowns (Ilancheran 2020). These issues affected subject enrollment, protocol adherence, trial operations, and data collection (Lasch et al. 2022). One analysis found an 80% year-on-year decrease in new patient enrollment for April 2020 (Xue et al. 2020). Pharmaceutical decision-makers triaged trials by devoting resources to the most promising studies and those with the least risk for patients (Colby et al. 2020). This decision ultimately led to the postponement or cancellation of planned studies and, in some cases, suspension or termination of ongoing studies (Xue et al. 2020).

To keep clinical trials going, minimize the risk of transmission of COVID-19, and preserve the continuity of care, data collection, and data integrity, many sponsors quickly deployed remote and virtual approaches (i.e., decentralized clinical trial (DCT) solutions), including eConsent, remote patient monitoring, data collection via wearable and mobile devices, and at-home assessments (Agrawal et al. 2021). Consequently, DCT deployments soared during the COVID-19 pandemic. The number of clinical trials with virtual and/or decentralized elements surpassed 1,000 in 2021 (a 50% increase compared with 2020), and 1,300 trials were forecasted to initiate in 2022 (Parkins and Hillman 2021).

DCT use in clinical trials promises to address a number of key drug development challenges. In addition to improving patient access and participation convenience, DCT solutions may also improve patient adherence to the protocol and may increase overall retention rates (Perry et al. 2019). DCTs enable clinical research data to be collected more easily and faster, offering the opportunity to interrogate and draw insights from the data sooner, reduce the number of patients required, and increase statistical power (Anderson et al. 2021). The deployment of remote and virtual solutions may also offer operational efficiencies through the automation of select manual data collection tasks, more frequent communication and interaction with study volunteers, and more productive investigative site personnel (Dorsey et al. 2020, Le Breton et al. 2020, Costello and Larrabee 2021).

Anecdotal reports and early case examples suggest that the promise of DCT use in clinical trials is being realized. Sponsors, contract research organizations (CROs), and DCT vendors have reported positive results with DCT deployments (Aitken 2017, PPD 2020, Anderson et al. 2021, Thoelke and Licholai 2021). For example, Sarraju et al. 2022 implemented a virtual study among atrial fibrillation patients, consisting of virtual recruitment via social media and virtual monitoring using a mobile application and sensors. Results showed high adherence, positive study engagement outcomes, and willingness to continue in a larger trial. Hilderbrand et al. 2021 conducted a 1,000-patient virtual clinical trial in just seven months at a fraction of the cost of a traditional site-based recruitment, demonstrating the benefits associated with reducing recruitment cycle times, and overall improvement in patient experience as patients reported satisfaction and willingness to move forward with the study. Overall, these cases exemplify the feasibility and benefits of a decentralized approach.

With growing deployment experience, some sponsors and CROs have reported challenges introduced by DCTs, including increasing clinical trial execution complexity, longer study start-up durations, and higher costs associated with installing technologies and infrastructure, offering training to site personnel and study volunteers, and providing technical support (Hilderbrand et al. 2021).

As more is learned – both positive and negative – about DCT use in clinical trials, sponsors and their collaborative partners face great difficulty in weighing benefits and risks and anticipating operating challenges. In this paper, we apply systems thinking to guide sponsors and CROs in comprehensively considering remote and virtual solutions – their advantages, pain points[1] addressed and introduced, and trade-offs – in protocol design and execution planning processes.

5.2 Methods

5.2.1 Defining DCT

[1] Pain points are recurring problems that inconvenience stakeholders. They emerge when system demands and pressures conflict with the stakeholder's attributes and constraints.

DCTs are broadly defined as clinical trials wherein recruitment and data collection are not restricted to centralized location(s) as is typical for conventional trials. Table 5.1 summarizes the more common DCT solutions in use today.

Table 5.1 DCT Solutions.

Element	Description
Digital health technologies	Technologies that track, monitor and capture participant health data and provide healthcare services including mobile device apps, wearables, bring your own device (BYOD), etc.
eConsent	Process that provides information about a study and obtains informed consent from study participants through a digital format
ePRO/eCOA	The capture of clinical outcome assessments (COA) such as participant reported outcomes (PRO) data through the use of electronic devices (e.g., e-diaries)
Virtual visits/eVisits/teleconsults	Consultations by remote telecommunications between a site investigator and a participant that take the place of in-person site visits
Mobile clinics and home health	Interventions and data collection by home healthcare professionals (HCPs) conducted in clinical trial visits that take place in a participant's home, workplace or mobile clinic in their community
Direct-to-patient IMP shipping	Delivery of IMP from a site, depot or pharmacy directly to a participant's home as well as the collection of specimens for laboratory testing and unused IMP for reconciliation and destruction

Among DCT deployments, there are two main variations: (1) DCTs that are entirely remote (full DCTs); and (2) DCTs that are partially remote (hybrid DCTs). Full and hybrid DCTs are achieved using telemedicine, digital health technologies, and approaches centralized around patient accessibility and convenience. The degree of decentralization can be assessed on two dimensions: the *locality* of the data capture (ranging from on-site research facilities to remote locations) and the *methods* for data collection (ranging through the use of intermediaries to fully virtual) (Khozin and Coravos 2019).

5.2.2 Analysis that Applies Systems Thinking

We applied systems thinking[2] to assess DCT deployment and its comprehensive interaction with the larger and complex process of clinical trial execution (Meadows 2008). Systems thinking takes a holistic perspective when considering problems and their solutions (Behl and Ferreira 2014).

[2] Since the coining of the term by Barry Richard in 1987, "systems thinking" has taken on various definitions (see (Arnold and Wade 2015) for a review of the literature). Many different systems thinking tools have emerged (e.g., root cause analysis, behavior over time graphs, and system dynamics, to name a few; see (Monat 2015) for a discussion of tools). Systems thinking has been applied in numerous domains, including healthcare.

A recent and relevant application of this approach is the "Engineering Better Care" systems framework that considered four interrelated perspectives (people, systems, design, and risk) to evaluate health and care design and improvement initiatives in an iterative and holistic way (Royal Academy of Engineering et al. 2017). Importantly, the framework considers stakeholders and their needs, the system architecture, a range of possible solutions that would help meet the needs of the system, and an assessment of what could go wrong/and can be improved. Applying a similar "whole system" approach, we consider how decentralization impacts clinical development.

Since a system is defined by its interconnections, a change in one element of the system invariably impacts other area(s) of the system. Thus, when a solution is introduced to alleviate a pain point for one or more stakeholders, it may introduce *new* system demands and pressures for other stakeholders. The emergence and alleviation of stakeholder pain points result in an iterative process that introduces new solutions, which then may add *new* system demands and pressures that lead to different pain points. Figure 5.1 captures this iterative process for DCT deployments (and its impact on participants, sites, and sponsors). It is worth mentioning that the system may include a wide range of stakeholders, such as contract research organizations (CROs), investigative sites, home HCPs, local care providers, regulators, institutional review boards, patient advocacy groups, payers, technology providers, couriers, and support services. The choice of focal stakeholders in the system depends on the purpose of the analysis and the goals one is striving to achieve.

This analysis helps to identify the appropriateness of DCT use in different settings based on the system's characteristics, such as the characteristics of the patient population, the disease, and the capacity and infrastructure availability. Various factors make certain studies or indications prime candidates for incorporating DCT solutions, which we will discuss in more detail.

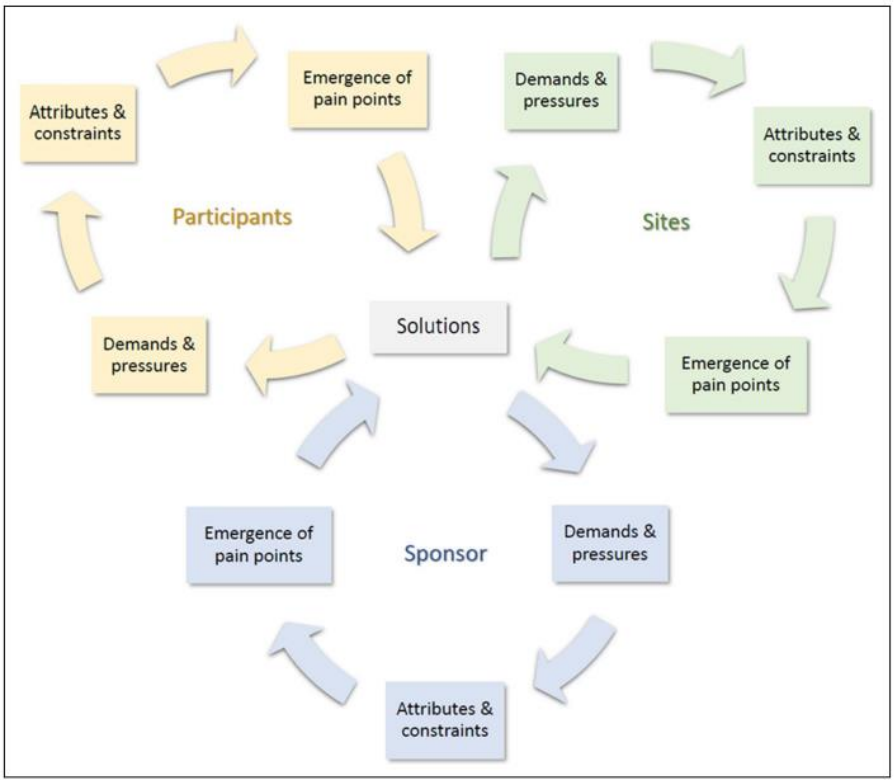

Figure 5.1 A systems view of pain points for participants, sites, and sponsors.

5.3 Results

Figure 5.2 presents the results of our assessment on the impact of DCT solutions using a systems thinking approach applied to a single stakeholder, the study participant. Based on literature review and anecdotal reports, we aim to cover many first-order effects.[3]

[3] The following discussion offers a broad and illustrative utilization of the framework. We note that different "systems" as defined by the scope (e.g., a small-scale, phase 1 cancer study) will have unique specificities that need to be considered. Future research can begin to characterize the framework's application to various systems.

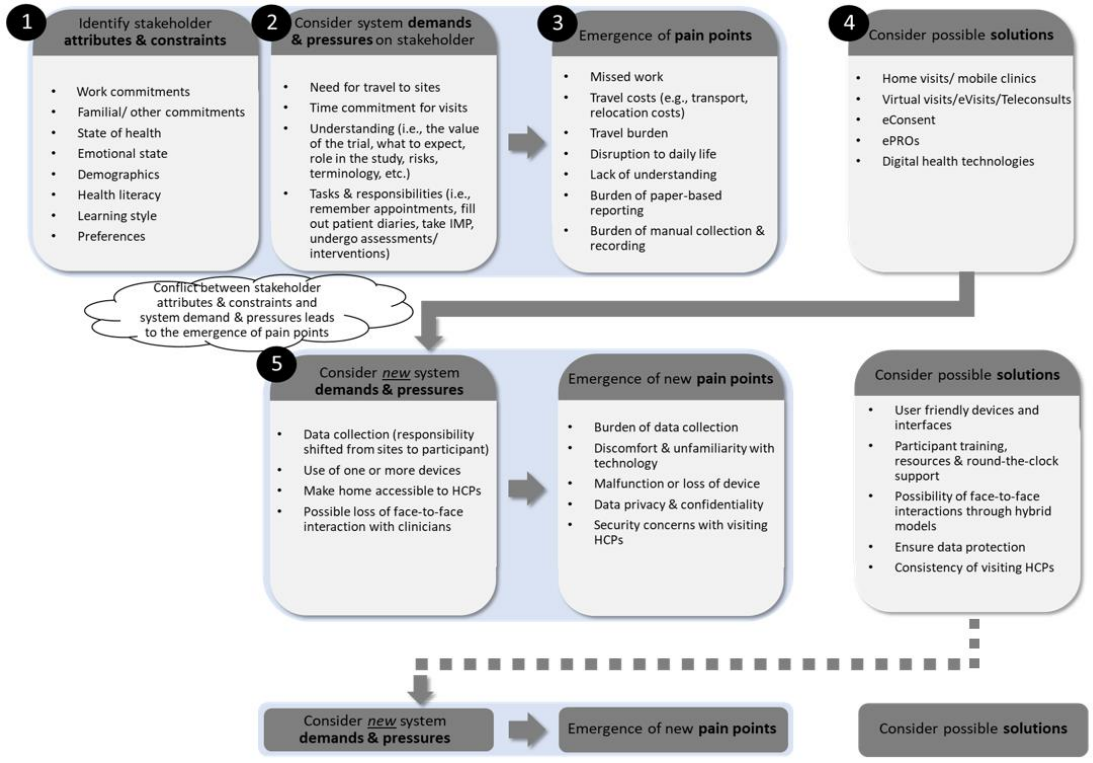

Figure 5.2 The process of emergence and alleviation of pain points for clinical trial participants.

Table 5.2 supplements the analysis by providing key advantages, disadvantages, and considerations for DCT elements that may serve as solutions to stakeholder pain points in this reiterative process.

Steps 1-3. The emergence of pain points. Clinical trial participants have individual *attributes* such as their state of health, demographics, and personal preferences, as well as *constraints* such as work, familial, and other commitments. Participation in a traditional site-centric clinical trial requires them to travel to sites for visits and develop an understanding of the trial (i.e., their role in the trial and the associated risks and relevant terminology). Moreover, participants have roles and responsibilities such as remembering and attending visits, undergoing assessments, and filling out patient diaries, to name a few. Resulting from the system design/architecture, these system *demands* and *pressures* may conflict with participants' attributes and constraints. For instance, consider a working single parent who may need to travel long distances to reach a site. Travel demands conflict with the participant's work and familial commitments, leading to a pain point.

Furthermore, this pain point can be particularly pronounced for participants from certain demographics (e.g., low socioeconomic status and those living in rural areas). One way to uncover the pain points incurred in trials is to map the patient journey (readers are referred to Trebble et al. (2010) for an introduction to mapping the patient journey). By capturing the sequence of events that a participant experiences when taking part in a clinical trial (from the point of view of the participant) sponsors can begin to identify the pressures and demands of participating in a trial.

Step 4. Possible solutions to alleviate pain points. There are many alternative solutions to alleviate stakeholder pain points. For example, financial compensation can be provided for missed work, reimbursements and stipends can be offered for travel costs incurred, and special travel can be arranged for participants with mobility issues. However, many of the pain points specified in Figure 5.2 can be alleviated through DCT elements (i.e., home visits & mobile clinics, virtual visits, eConsent, ePROs, and digital health technologies).

Step 5. Introduction of new system demands & pressures. Many DCT solutions – including the use of mobile devices and home-based assessments – transfer execution responsibility away from what was historically handled by site personnel to the participants themselves. If this demand conflicts with participants' attributes (i.e., digital literacy, demographics) and/or preferences, this may lead to the emergence of pain points. In turn, new solutions may need to be introduced to address emerging pain points (e.g., discomfort with technology can be alleviated through participant training, round-the-clock support, etc.). Successive solutions present new demands and pressures, leading to new pain points.

Iterative steps. Minimization and management of pain points. By repeating Steps 2-5 multiple times, decision-makers can evaluate the emergence and alleviation of pain points in applying various solutions.

The resulting analysis and insights can allow decision-makers to identify ways to minimize or mitigate stakeholder pain points so that, ultimately, more value can be created from implementing DCT solutions.

DCT solutions identified for the participant analysis in Figure 5.2 also address and alleviate pain points faced by sites (e.g., administrative burden and paperwork, errors from manual data entry, the workload associated with menial tasks stemming from site visits, etc.) and sponsors (large investigator grant payments, recruitment and retention issues, among others).

However, by the systems view approach, such solutions may also introduce new demands and pressures onto stakeholders. Demands and pressures should again be assessed alongside all stakeholders' attributes and constraints, and a similar process to the one illustrated in Figure 5.2 should be performed for all key stakeholders.

Table 5.3[4] provides a sample of the new demands and pressures experienced by participants, investigative sites, and sponsors from the introduction of various DCT solutions. DCTs deployments require the use of new technologies, new stakeholders and new stakeholder roles in the provision of care, and data collection outside of traditional investigative sites. Thus, demands and pressures arise from the two dimensions of decentralization (digitalization and locality) (Khozin and Coravos 2019) introduced earlier, and can be broadly grouped into four categories: the introduction of new technology, reliance on staff outside of sites, a greater reliance on the participants themselves, and changes to the supply chain.

Multiple detailed and holistic iterations designed to alleviate stakeholder pain points culminate insight into primary advantages such as a reduction in site burden, enhanced access and increased diversity, improved external validity of findings, and possible cost savings. However, the demands and pressures imposed by DCT solutions on clinical trial systems also amount to several overarching challenges, including potential inequalities, privacy and data protection issues complex operational requirements[5]. Despite these challenges, enablers (such as growing regulatory agency commitment and digital advances) moderate the degree to which the new demands and pressures actualize into pain points and, therefore, continue to spur demand for DCT solutions. A detailed discussion on the advantages, disadvantages, obstacles, and enablers associated with DCTs can be found in the Appendix.

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[4] Table 5.3 provides a non-comprehensive list of possible pain points. We also refer the reader to Apostolaros et al. 2020, who outline the key stakeholder challenges to implementing DCTs as indicated in group interviews and an expert meeting of more than 50 diverse industry representatives.

Table 5.2 DCT solutions – Advantages and challenges mapping

Element	Potential advantages	Potential challenges & considerations
Digital health technologies	-**Improved patient outcomes**[i] -Generation of more comprehensive **real-time data** in a **real-world** setting -Rapid handling of issues such as adverse events through **real-time monitoring** -**Reduced need for on-site visits** (this has time and effort implications for participants and site personnel) -**Enhanced patient experience**[ii] -**Increased participant convenience**: e.g., with wearables, participants do not have to manually collect and record data -**Higher patient engagement**: e.g., patients can be more active in their care and better understand how their behaviors can affect their health in real-time (Bove 2019)	-Management, interpretation and analysis of **large amounts of data** -**Incorrect use/malfunction/loss** of device -**Increased participant burden**: shifting burden of data collection from site personnel to participant (especially worrisome for naive trial participants or if participant needs to use several devices for a study) -Level of **oversight and environmental control** -Ensure **data privacy and security** -**Cost** considerations: e.g., provisioning devices requires purchase and shipping, storage, distribution (to sites and participants), maintenance and replacement costs for the sponsor (Gwaltney et al. 2015) -**Regulatory** considerations: technology needs to be qualified to capture high-quality clinical data -**Operational** considerations: e.g., how to incorporate technologies into the protocol, appropriateness of technologies for the study, technology obsolescence (especially for longer studies), etc.
eConsent	-**Improved traceability** through date and time stamps -**Improved participant comprehension**[iii] -Consent in the **comfort** of participants' homes[iv] -**Reduced errors** such as incomplete consent forms leading to protocol deviations -**Less administrative burden** and paperwork for sites -**Ease of updating** consent forms and obtaining re-consent after protocol amendments	-**Resistance to adoption** by healthcare professionals -**Financial and time investment** (such as site personnel training) -**Changes in existing processes and workflows** -**Evaluation of vendors**' solutions and support (provided to participants and sites)
ePRO/eCOA	-Eliminates or **reduces missing/inappropriate/out-of-range responses** through limits and controls on data entry -**Ensures timely completion** by reducing "parking-lot compliance" and forward filling through alerts to participants and specified time windows for data entry[v] -**Reduces patient and site burden** associated with maintaining paper-based diaries -Permits **faster data processing and analysis** through automatic upload of data. This can also quickly alert sites when there is a reduction in compliance based on ePROs	-**Technical problems** potentially leading to the loss of data, reduction in participant compliance and/or participant experience -**Time, cost, and resources** required for **training and supporting participants** in using electronic diaries -Differences in **participants' comfort with digital technologies** and computer literacy
Virtual visits/ eVisits / Teleconsults	-**Reduced need for participant travel** (this has implications for **reducing participant burden** as well as **enhancing participant reach**, i.e., for those in certain geographic areas, those with disabilities, etc.) -**Improved infection control** (especially relevant for studies involving immunocompromised participants) -Potential for **better assessment**[vi]	Ftouni et al. 2022 provide a systematic review of the challenges with telemedicine. These include **technical issues** (including **lack of universal access** to technology, poor connection which hampers communication), **privacy and confidentiality** (e.g., cybersecurity risk), **lack of physical examination** (especially for complex procedures and specialized assessments), special populations (e.g., **digital literacy** in certain age groups, **demographic disparities**), **training** of providers and patients, **need for face-to-face interaction** in establishing rapport (especially when subjects are participating in a clinical trial for the first time)
Mobile clinics & home health	-Enhanced **patient centricity**: less disruption to participants' lives -**Reduced burden** (of performing more routine activities such as blood draws) on sites -**Increased access** to clinical trials to underserved communities -Home administration of investigational medicinal product (IMP) that is **representative of real-world administration** once approved	-**Feasibility** of home care (dependent on phase, type of indication, need for equipment and physical infrastructure, patient population) -Home HCP's **qualifications, scope of practice and training**: e.g., Good Clinical Practice, adverse event (AE) reporting, data protection -**Patient preference**: e.g., security concerns regarding visiting home HCPs -**Operational** considerations: e.g., sample stability in transit, technology or equipment failure (mobile or home HCPs do not have access to immediate expert assistance/supplies), responsibility for oversight of home HCP -**Consistency** of data collection across sites and home HCPs -Sponsor's **cost** considerations (dependent on type of HCP needed, training, etc.)
Direct-to-patient IMP shipping	-**Facilitates the conduct of trial visits outside of sites** (i.e., through home visits, virtual visits, etc.) which has implications for participants' need to travel, disruption to lives, patient experience, and participant recruitment and retention	-Participant **confidentiality and privacy** -**Feasibility**: depends on IMP's stability and shelf-life, risk profile, dosing frequency, route of administration, special preparation vs. ready-to-use, ease of administration -**Accountability/traceability/chain of custody** -Ensure IMP is delivered in **good quality** (drug integrity and temperature control) -**Participant compliance**: e.g., if IMP is self-administered, is patient storing/administering/safeguarding/disposing the drug correctly? -Compliance with regional, state, national **laws and regulations** (where IMP is dispensed and received) -**Costs**: e.g., shipping, inventory, wastage, specialized couriers, ability to pool supply -**Coordination:** e.g., arrival window of delivery may need to be coordinated with home HCP visit to administer the IMP

[i] As summarized in McKenna et al. (2021), various studies have shown such technologies are associated with enhanced outcomes such as greater weight loss (in a weight loss intervention study) and improved drug adherence.

[ii] In comparing BYOD to paper records and a provisioned device, Byrom et al. (2018) find 94% of subjects would definitely or probably be willing to download an app onto their own mobile device for a forthcoming clinical trial with 45% expressing that BYOD would be more convenient compared with 15% preferring a provisioned device. Note that BYOD eliminates the need to carry and maintain a second device for the duration of the study.

[iii] Through the use of multimedia such as images, video, audio (e.g., in multiple languages), quizzes, electronic glossaries, etc. the consent process can be interactive, engaging and tailored to the trial subjects' demographics and participants' learning styles (Godwin-Smith 2022, Horsey 2022).

[iv] This can allow participants more time for consideration, thereby reducing the pressure for immediate consent and allows for family and caregivers to be involved in the review process (Sather 2018).

[v] "Parking-lot compliance" refers to the notion of participants filling in their entire diary immediately prior to a study visit whereas forward filling refers to participants entering the data prior to the scheduled time (Jhaveri and Lee 2007).

[vi] Telemedicine can allow specialists to see participants in their home environments, e.g., allergists may be able to identify clues in the patients surroundings that cause allergies (Hasselfel, 2022).

Table 5.3 A sample of the new demands and pressures introduced by DCT solutions and resulting pain points faced by sponsors, sites, and participants.

Demands and Pressures from DCT Solutions	Stakeholder	Pain Point
Introduction of new technology	Sponsor	- Payments to technology vendors - Expensive technology - No available technology to meet needs - Implementation costs - Training and upskilling needs of sites, CROs, home HCPs, other personnel - Data integration (of data coming in from multiple sources) - Inconsistent state telemedicine laws - Ensuring privacy and confidentiality
	Sites	- Training burden - New or altered standard operating procedures - Additional workload (esp. with hybrid trials) - Oversight: Verifying participants' identities - Oversight: Adequately gauging participants' understanding - Ensuring privacy and confidentiality
	Participant	- Difficult and/or inconvenient to use - Malfunction or loss of device - Data privacy and confidentiality
Reliance on mobile clinic and home HCP vendors	Sponsor	- Payments to mobile clinic/ home HCP vendors - High turnover of home nursing staff - Varying medical qualifications of mobile/home HCPs - Inconsistencies in knowledge of the protocol of mobile/ home HCPs
	Sites	- Oversight of source documents - Acceptance of external staff (e.g., home HCPs) - Worry that they will be cut out of the process (affecting investigator payments)
	Participant	- Security concerns and discomfort with home visits
Reliance on participants	Sponsor	- Oversight: Adverse event reporting through remote technologies - Oversight: Ensuring data integrity and safety monitoring
	Sites	- Oversight: Ensure digital health technologies used by participant and not someone else - Oversight: Ensure digital health technologies used correctly and as intended - Oversight: Ensure data is recorded properly and truthfully
	Participant	- Desire for face-to-face interactions with HCPs and clinical experts - Burden of data collection - Concern of being unequipped for new responsibilities and tasks
New supply chain vendors	Sponsor	- Payments for direct-to-patient IMP shipping/couriers - State differences for direct shipping of IMP to participants

[5] One such example relates to the significant supply chain changes required to facilitate drug logistics and management to multiple coordinating locations, including patients' homes. This "last-mile logistics" brings upon new challenges and necessitates a high degree of coordination across many stakeholders operating in different supply chain areas and various geographies. The issue of complexity also materializes in IT infrastructure and vendor management. The abundance of emerging technological solutions and vendors has raised concerns regarding vendor selection, ease of integration, and interoperability of systems. Moreover, due to data in DCTs coming in from a wide range of sources, the complexity of data transfer, compilation, interpretation, analysis, and management has intensified. Such difficulties threaten the promise of DCTs and diminish the associated advantages.

5.4 Discussion

What becomes apparent through systems thinking analysis is that the appropriateness of DCT use differs depending on system characteristics. Various factors make certain studies or indications prime candidates for incorporating DCT solutions. Discomfort and unfamiliarity with technology is a participant pain point associated with the digitalization component of DCTs. For sites and sponsors, important considerations include constraints relating to the specifics of the study (e.g., the therapeutic area, the phase of the trial, the incidence and prevalence of disease, etc.), national and international regulatory environment, existing resources and infrastructure (e.g., staff, equipment, technology, competencies, procedures, etc.), and the budgets for clinical trial conduct.

Clinical Trials Arena has tracked the distribution of different DCT categories by therapy area (Fultinavičiūtė and Maragkou 2023). The analysis finds that telemedicine and remote monitoring are the most widely accepted DCT components across therapy areas. Telemedicine has been used the most in infectious disease and oncology trials, while, perhaps not surprisingly, remote monitoring (using sensors, device, and trackers) has been prominent in cardiovascular, central nervous system, and metabolic disorder trials. Moreover, due to the regulatory and operational requirements brought about by the COVID19 pandemic, COVID-19 drug trials were the most likely to use remote drug delivery and remote nursing (Fultinavičiūtė et al. 2023). The research finds that dermatology and women's health trials have most often incorporated ePROs, eCOAs, or eConsent. It is noted that the complexity of disease may limit the uptake of such components in oncology trials. Furthermore, data from eCOA may be less important for certain therapy areas, such as cardiovascular and metabolic disorders, that are more concerned with physiological measurements as key endpoints rather than reported outcomes (Fultinavičiūtė and Maragkou 2023). This highlights a key point alluding to the quote "just because you can, doesn't mean you should." Even though a DCT element may be easily incorporated into a trial, the appropriateness to do so depends on the value it creates for the system.

Demands and pressures imposed by DCT solutions may be more aligned with certain attributes, thus leading to fewer (and less pronounced) pain points. For example, the therapeutic area and the types of assessments required for the trial are two critical constraints. Degenerative conditions

whereby travel for even short distances is especially burdensome (Kutzing and Deglincerti 2021) or areas such as stroke management, where patients can manage their disease condition relatively easily, and dermatology, in which telemedicine (and video consultation) is suitable and already well-utilized (Apostolaros et al. 2020), may be most appropriate for DCT solutions. Similarly, sleep studies conducted at home can provide more informative data and better facilitate patient preferences (Fantana et al. 2022). Such studies may be good candidates for the early adoption of most DCT elements. They can also pave the way for other indications by exemplifying the implementation processes and lessons learned.

Clinical trials in oncology and infectious diseases, on the other hand, in which the safety of the investigational drug is not well characterized and require tests that can only be performed in medical facilities (e.g., magnetic resonance imaging) (Friend 2022) are unfavorable candidates for *complete*[6] decentralization. In these cases, DCTs should be treated as one of the many resources that drug development stakeholders can add to their toolbox, and the decisions in choosing the right DCT elements for a hybrid trial approach become paramount.

Sites and sponsors will also consider the operational requirements of the study (e.g., dosing frequency, method of administration, investigational drug storage requirements, to name a few) as well as whether there exists appropriate and validated technology and if the infrastructure is (or can easily be) established. Moreover, the regulatory environments in which DCTs will take place must be carefully evaluated. Different geographies may have different laws and regulations regarding telemedicine and direct-to-patient shipping of IMP and be more or less receptive to trial decentralization.

A key insight of the research is that DCTs enable a departure from a "one-size-fits-all" model of conducting clinical trials and facilitate patient-centered care. Through standard procedures and processes, centralized trials have the advantage of attaining operational efficiencies for sites and sponsors. However, as previously discussed, the challenges with centralization can deter participants from joining and/or remaining in clinical trials, thus negatively impacting enrollment

[6] Complete decentralization may not currently be feasible. However, this could change as technologies mature and become more widely accessible. For instance, new biomarkers have emerged and are increasingly used in oncology. One such example is circulating tumor DNA (ctDNA). A major advantage of ctDNA analysis is that samples are extracted non-invasively through blood collection. This could reduce the need for on-site visits for tissue biopsies.

and retention rates. To address these concerns, pharmaceutical companies have typically relied on monetary compensation as a key form of incentivization. A recent study shows that participants of 1-2 phase I clinical trials earned, on average, $4, 000 USD annually (Fisher et al. 2021). Although participants' motivations are not limited to financial incentives (for instance, other motivations include a contribution to science and the health of others, accessing ancillary healthcare benefits, meeting people, etc.), financial reward is the primary motivation for healthy volunteers (Stunkel and Grady 2011). Payments in the form of compensation for missed work and reimbursements and stipends for incurred travel costs can be considered as blunt instruments to overcome centralization issues (such as time commitments and geographical barriers). Analogous to pain killers, financial rewards alleviate participants' pain points associated with trial participation in traditional site-centric studies. However, this approach *treats the symptoms and not the disease*. As demonstrated in Section 5.3, pain points vary across participants. DCTs allow sponsors to target the root causes of pain points directly. By offering a menu of "treatments" or DCT elements (i.e., home visits & mobile clinics, virtual visits, eConsent, ePROs, and digital health technologies), sponsors can conduct more patient-centric trials. This is especially true for hybrid trials which grant participants the most choice in how they can participate. However, as with any treatment, DCTs also have "side-effects" that need to be considered. As previously noted, the introduction of DCT elements places new demands and pressures onto the existing system which can lead to pain points experienced by different system stakeholders (refer to Table 5.3). Taken together, moving away from a broad financial solution to a patient-specific approach could offer an opportunity for sponsors to recruit and retain participants without having to bear steep compensation costs. However, as discussed in the Section 5.3 and in the Appendix, DCTs may introduce operational challenges and new costs that may offset the cost reduction associated with lower participant compensation. As will be further discussed, the change in operational model needs to be evaluated on several dimensions. Whilst DCTs offer much promise, acknowledging and addressing the drawbacks and challenges of DCTs is key to their successful deployment.

In thinking about how to scale and ensure the longevity of DCTs, it is crucial that appropriate solutions are deliberately selected and tailored to align with the specifics of the system prior to implementation. This contrasts the early phases of DCT use in the pandemic where, to a certain extent, solutions were "shoehorned" into existing systems (Riches 2022). A key aspect of this is a

consideration of the partner ecosystem. Looking across the system, tensions may appear when the costs and benefits stemming from DCT implementation are not shared equally. One question that arises is whether the industry is stretched in two directions: offering patient choice versus the pursuit of operational excellence (i.e., executing trials faster and cheaper) (Young 2022). The greater the alignment between such conflicting factors, the easier it is to ensure the sustainability of DCTs. This may necessitate building certain capabilities causing stakeholder roles to shift (e.g., consider, for example, the rising industry demand for data scientists) (Riches 2022). It is important to recognize that to minimize implementation challenges, trade-offs and pain points need to be recognized and mitigated. The systems approach presented in the paper offers stakeholders a way of holistically examining the impact of DCTs on the system: the implications for themselves and as well as on their partners. Each stakeholder needs to ask themselves a series of questions: (i) What problem do we want to solve?; e.g., increase participation in a clinical trial, reduce costs, speed up data collection, etc. (ii) Who are the stakeholders and partners? Which organizations could we approach? (iii) Why do we approach this problem using a DCT?; e.g., disease profile, patient profile, etc. (iv) How can we overcome the challenges? What are we good at, and what do we need to improve?

5.5 Conclusion

Although the many possibilities offered by DCTs underscore strong industry interest in trial decentralization, without detracting from the promise of DCTs, we urge caution in the widespread application of DCT solutions absent a thorough systems-oriented consideration of their impact on the clinical trial operating environment.

The current operating environments calls for heightened awareness and demand for solutions that can simplify the clinical development process for staff and patients. There is no doubt that DCTs will be a part of that effort. A recent survey found that most biopharma respondents viewed DCTs favorably (Lamberti 2022). However, how DCTs are implemented and incorporated into existing clinical research paradigms remains to be seen.

At the current state of DCT adoption, many organizations, surveys, and roundtables reveal that customized hybrid trials are thought to be the most viable option (Sarraju et al. 2022, Hilderbrand et al. 2021). We believe a "all-encompassing" approach is inappropriate even as DCT adoption reaches maturity. As seen through the systems thinking framework, any such incorporation has wide-ranging impacts on key stakeholders and should be carefully considered. DCT solutions should be treated as one of the many tools that drug development stakeholders can add to their arsenal as they look for ways to make clinical research more relevant and accessible to a larger and more diverse[7] patient population.

To ensure that decentralization can enable diversity in clinical research, DCT solutions (and the resulting demands they place onto a diverse participant population) should be assessed to confirm that patients from diverse backgrounds are being included. Moreover, digital elements should be coupled with high-quality support and training to increase participants' comfort and willingness to use technology. Importantly, clinical trials need to be designed to include accommodating options that meet a variety of patient preferences (and factor in various considerations such as participants' socio-economic status). The resulting downstream impact (e.g., effect on data collection and data quality) of this level of customization should also be evaluated. Reinforced by a recent push from regulators (Kozlov 2023, Armstrong 2023) to increase diversity in clinical testing, well-designed studies incorporating DCT solutions may offer a way to address under-representation in clinical research by removing some of the barriers associated with traditional clinical trials (Goodson et al. 2022).

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[7] The adoption of DCT into clinical trials can help reduce some of the major barriers related to participation among underrepresented and marginalized groups, such as racial minorities. For instance, there is a common perception that a major reason why Black participants do not participate in clinical research is due to mistrust in medical science related to past ethical violation. Yet, recently, researchers have shown that mistrust related to past ethical violation was not a major reason for the lack of Black patients in clinical studies (Liu et al. 2023). Lack of accessibility, limited access to specialty care, and time have been identified as barriers for participation among racial minorities (Liu et al. 2023). By reducing geographic barriers, DCTs can help increase opportunities for racial minority patients to participate in clinical research. However, this needs to be coupled with health system transformations which promote a racially/ethnically diverse healthcare workforce, diversity, equity, and inclusion training for clinicians, and initiatives that foster community engagement and partnerships to engage diverse populations (Borno et al. 2021). It is important to note that the benefits of DCTs may be limited for marginalized groups who, for example, do not have access to smart phones, internet, and/or lack a certain degree of digital literacy.

Systems thinking can assist decision-makers in assessing the system effects of DCTs. In choosing the best candidates and elements for DCT implementation, the framework may reveal different insights for different systems corresponding to their unique characteristics and, importantly, can be used to shed light on the appropriateness of DCT use and where there may be shortfalls. If a DCT solution leads to the emergence of more non-actionable pain points than the number of pain points it alleviates, one should be cautious in its steadfast acceptance and implementation. This approach can help the industry adopt solutions with higher chances of success and create best practices for implementation early on. This will pave the way for introducing potentially more complex elements and solutions by solving any technology and infrastructure-related issues upfront.

Recent trends indicate growing regulators' commitment toward DCTs, laying the groundwork for regulatory guidance and oversight on the adoption of DCT (Agrawal et al. 2021). Indeed, the COVID-19 pandemic has resulted in increased and quickly evolving regulatory acceptance of decentralized interventions. Furthermore, the pandemic has helped improve attitudes toward digital health solutions and has heightened stakeholder comfort levels with digital technologies, which can undoubtedly reinforce the continued adoption of DCTs where appropriate.

In conclusion, despite the enthusiasm surrounding the adoption of DCTs in clinical research, more robust research is needed to quantify the impact of DCTs empirically. The systems thinking framework provides a systematic and reiterative way to identify pain points and assess possible solutions through DCT implementation. A natural subsequent step is to devise new research that quantifies the impact of introducing DCT elements to various systems by considering the value generated for different stakeholders. To that end, we encourage and invite opportunities to collaborate with industry stakeholders to investigate a range of topics, ranging from mapping the types of operational models related to drug distribution and management, developing a scoring tool to systematically apply DCT elements and solutions to clinical trials for various conditions, to classifying the different types of devices used and examining their impact on patient experience.

References

ACRO (Association of Clinical Research Organizations). 2020. Decentralizing clinical trials: A new quality-by-design, risk-based framework. Available at: https://www.acrohealth.org/dctwhitepaper/. Accessed October 6, 2022.

Aitken, M. 2017. The growing value of digital health: Evidence and impact on human health and the healthcare system. *IQVIA Institute.* Available at: https://www.iqvia.com/insights/the-iqvia-institute/reports/the-growing-value-of-digital-health. Accessed December 29, 2022.

Agrawal, G., J. Xue, R. Moss, et al. 2021. No Place Like Home? Stepping Up the Decentralization of Clinical Trials. *McKinsey & Company.* Available at: https://www.mckinsey.com/industries/life-sciences/our-insights/no-place-like-home-stepping-up-the-decentralization-of-clinical-trials. Accessed October 6, 2022.

Alexander, W. 2013. The uphill path to successful clinical trials. *Pharmacology & Therapeutics* 38(4):225–27.

Anderson, D., J. Fox, N. Elsner. 2018. Digital R&D: Transforming the future of clinical development. *Deloitte*. https://www2.deloitte.com/us/en/insights/industry/life-sciences/digital-research-and-development-clinical-strategy.html. Accessed October 6, 2022.

Apostolaros, M., D. Babaian, A. Corneli, et al. 2020. Legal, regulatory, and practical issues to consider when adopting decentralized clinical trials: Recommendations from the clinical trials transformation initiative. *Therapeutic Innovation & Regulatory Science* 54:779–87.

Applied Clinical Trials. 2022. Where does direct-to-patient fit in a post-COVID world? Available at: https://www.appliedclinicaltrialsonline.com/view/where-does-direct-to-patient-fit-in-a-post-covid-world. Accessed October 6, 2022.

ArcheMedX. 2022. DCTs at risk, or ready? Assessing the risk and readiness of your next clinical trial. February 2022- SCOPE Summit. Available at: https://www.info.archemedx.com/hubfs/SCOPE2022%20Whitepaper%20%20DCTs%20at%20Risk%20or%20Ready.pdf?hsLang=en. Accessed 6 October 2022.

Armstrong A. 2023. FDA Encourages Decentralized Trials with New Guidance. Fierce Biotech. https://www.fercebiotech.com/biotech/fda-encourages-decentralized-trials-new-guidance. Accessed May 3, 2023.

Arnold, R.D., J.P. Wade. 2015. A definition of systems thinking: A systems approach. *Procedia Computer Science* 44:669–78.

Banks, M.A. 2021. In the wake of COVID-19, decentralized clinical trials move to center stage. *PNAS* 118(47):e2119097118.

Behl, D.V., S. Ferreira. 2014. Systems thinking: An analysis of key factors and relationships. Procedia Computer Science 36:104–9.

Bestsennyy, O., G. Gilbert, A. Harris, et al. 2021. Telehealth: A quarter-trillion-dollar post-COVID-19 reality? *McKinsey & Company*. Available at: https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/telehealth-a-quarter-trillion-dollar-post-covid-19-reality. Accessed October 6, 2022.

Betcheva L., F. Erhun, H. Jiang. 2020. Supply chain thinking in healthcare: lessons and outlooks. *Manufacturing &Service Operations Management* 23(6):1333–53.

Betts, D., L. Korenda, S. Giuliani. 2020. Are consumers already living the future of health? *Deloitte.* https://www2.deloitte.com/us/en/insights/industry/health-care/consumer-health-trends.html. Accessed October 6, 2022.

Bove, L.A. 2019. Increasing patient engagement through the use of wearable technology. The Journal for Nurse Practitioners 15:535–539.

Byrom, B., H. Doll, W. Muehlhausen, et al. 2018. Measurement equivalence of patient-reported outcome measure response scale types collected using bring your own device compared to paper and a provisioned device: Results of a randomized equivalence trial. *Value Health* 21(5):581–589.

Chaudhari, N., R. Ravi, N. Gogtay, et al. 2020. Recruitment and retention of the participants in clinical trials: challenges and solutions. *Perspectives in Clinical Research* 11(2):64–9.

CISCRP (Center for Information and Study on Clinical Research Participation). 2019.Perceptions and insights study. Available at: https://www.ciscrp.org/wp-content/uploads/2019/12/Deciding-to-Participate-04DEC-.pdf. Accessed October 6, 2022.

Clark, L.T., L. Watkins, I.L. Piña, et al. 2019. Increasing diversity in clinical trials: Overcoming critical barriers. *Current Problems in Cardiology* 44(5):148–172.

Clinical Leader. 2022. Considerations for improving patient recruitment into clinical trials. Available at: https://www.clinicalleader.com/doc/considerations-for-improving-patient-0001. Accessed October 6, 2022.

Colby, J., R. Breiten. The COVID-19 clinical landscape and its impact on clinical research and the biopharmaceutical sector. *Pharm-Olam*. Available at: https://www.pharm-olam.com/blog/pharm-olam-releases-updated-paper-on-the-impact-of-covid-on-clinical-research. Accessed October 6, 2022.

Coran, P., J.C. Goldsack, C.A. Grandinetti, et al. 2019. Advancing the use of mobile technologies in clinical trials: Recommendations from the clinical trials transformation initiative. *Digital Biomarkers* 3(3):145–54.

Costello, M., P. Larrabee. 2021. Sites still necessary for decentralized trials. *Applied Clinical Trials.* Available at: https://www.appliedclinicaltrialsonline.com/view/sites-still-necessary-for-decentralized-trials. Accessed December 29, 2022.

Dizon D.S., C.M. Szczepanek, D.P. Petrylak, et al. 2022. National impact of the COVID-19 pandemic on clinical trial staff attrition: results of the SWOG cancer research network survey of oncology research professionals. *Journal of Clinical Oncology* 40(16 suppl):11049.

Dorsey, E., B. Kluger, C. Lipset. 2020. The new normal in clinical trials: Decentralized studies. *Annals of Neurology* 88(5):863–866.

DTRA. 2021. Decentralized trials & research alliance. Available at: https://www.dtra.org/. Accessed October 6, 2022.

EMA. 2020. Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic. Available at: https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic. Accessed on October 6, 2022.

Fantana, T., A. Combs, J. Li. 2022. How remote patient monitoring technology can impact decentralized clinical trials. *Applied Clinical Trials*. Available at: https://www.appliedclinicaltrialsonline.com/view/how-remote-patient-monitoring-technology-can-impact-decentralized-clinical-trials. Accessed November 2, 2022.

FDA. 2022. About the digital health center of excellence. Available at: https://www.fda.gov/medical-devices/digital-health-center-excellence/about-digital-health-center-excellence. Accessed October 6, 2022.

FDA. 2021. FDA guidance on conduct of clinical trials of medical products during the COVID-19 public health emergency. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency. Accessed October 6, 2022.

Fisher, J.A., L. McManus, J.M. Kalbaugh, R.L. Walker. 2021. Phase I trial compensation: How much do healthy volunteers actually earn from clinical trial enrollment? *Clinical Trials* 18(4): 477–87.

Florence Healthcare. 2022 State of clinical trial operations technology report. Available at: https://florencehc.com/learn/ebinders/2022-state-of-clinical-trial-operations-technology-report. Accessed October 19, 2022.

Florence Healthcare. 2022. 9 Challenges and risks for launching decentralized trials. Available at: https://florencehc.com/learn/blog-posts/9-challenges-and-risks-for-launching-decentralized-trials. Accessed October 6, 2022.

Friend, K. 2022. Decentralized clinical studies: What does the future look like? *Imperial Clinical Research Services.* Available at: https://www.imperialcrs.com/blog/2022/08/08/what-is-the-future-of-decentralized-clinical-studies/. Accessed November 2, 2022.

Ftouni, R., B. AlJardali, M. Hamdanieh, et al. 2022. Challenges of telemedicine during the COVID-19 pandemic: A systematic review. *Medical Informatics and Decision Making* 22:207:1–23.

Fultinavičiūtė U., I. Maragkou. DCT Adoption tracker: Exploring trial decentralisation Archetypes by therapy area. *Clinical Trials Arena*. https://www.clinicaltrialsarena.com/features/dct-adoption-archetype-therapy-area/. Accessed May 1, 2023.

Fultinavičiūtė U., I. Maragkou, R. Castañeda, et al. 2023. DCT tracker: Tracing industry's adoption of decentralised clinical tTrials. *Clinical Trials Arena*. https://www.clinicaltrialsarena.com/analysis/dct-adoption-tracker-who-and-what-is-at-the-crestof-the-trial-decentralisation-wave/. Accessed May 1, 2023.

Gao, F., M. Solomon, A. Roy, et al. 2021.Why decentralized clinical trials are the way of the future. *Applied Clinical Trials.* Available at: https://www.appliedclinicaltrialsonline.com/view/why-decentralized-clinical-trials-are-the-way-of-the-future. Accessed December 29, 2022.

Galsky, M.D., K.D. Stensland, R.B McBride, et al. 2015. Geographic accessibility to clinical trials for advanced cancer in the United States. *JAMA Internal Medicine* 175(2):293–5.

Getz, K.A., V. Sethuraman, J. Rine, et al. 2019. Assessing patient participation burden based on protocol design characteristics. *Therapeutic Innovation & Regulatory Science* doi:10.1177/2168479019867284.

Getz, K.A., R.A. Campo. 2018. New benchmarks characterizing growth in protocol design complexity. *Therapeutic Innovation & Regulatory Science* 52(1):22–8.

Getz, K.A. 2014. Improving protocol design feasibility to drive development economics and performance. *International Journal of Environmental Research and Public Health* 11(5):5069–80.

Getz, K., Z. Smith, M. Kravet. 2014. Protocol design and performance benchmarks by phase and by oncology and rare disease subgroups. *Therapeutic Innovation & Regulatory Science* doi.org/10.1007/s43441-022-00438-5.

Godwin-Smith, K. 2022. eConsent in Clinical Research: Overcoming the Challenges of Protocol Amendments. Technology Networks Drug Discovery. Available at: https://www.technologynetworks.com/drug-discovery/articles/econsent-in-clinical-research-overcoming-the-challenges-of-protocol-amendments-363324. Accessed October 6, 2022.

Goodson, N., P. Wicks, J. Morgan, et al. 2022. Opportunities and counterintuitive challenges for decentralized clinical trials to broaden participant inclusion. *NPJ Digital Medicine* 5(58):1–6.

Grand View Research. 2022. Digital health market size & share report. Available at: https://www.grandviewresearch.com/industry-analysis/digital-health-market. Accessed October 6, 2022.

Guerrero, S, A. López-Cortés, A. Indacochea, et al. 2018. Analysis of racial/ethnic representation in select basic and applied cancer research studies. *Scientific Reports* 8(1):1–8.

Gwaltney, C., S.J. Coons, P. O'Donohoe, et al. 2015. "Bring your own device" (BYOD): The future of field-based patient-reported outcome data collection in clinical trials? *Therapeutic Innovation & Regulatory Science* 49(6):783–91.

Halloran, L. Can virtual trials maintain their momentum after COVID? *Clinical Leader.* Available at: https://www.clinicalleader.com/doc/can-virtual-trials-maintain-their-momentum-after-covid-0001. Accessed October 6, 2022.

Hamel, L., A. Kearney, A. Kirzinger, et al. 2020. KFF Health Tracking Poll- May 2020. *Henry J. Kaiser Family Foundation.* Available at: https://www.kff.org/report-section/kff-health-tracking-poll-may-2020-health-and-economic-impacts/. Accessed October 6, 2022.

Hargreaves, B. 2016. Clinical trials and their patients: The rising costs and how to stem the loss. *Pharmafile.* Available at: http://www.pharmafile.com/news/511225/clinical-trials-and-their-patients-rising-costs-and-how-stem-loss. Accessed October 6, 2022.

Hasselfeld, B.W. 2022. Benefits of telemedicine. *Johns Hopkins Medicine.* Available at: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/benefits-of-telemedicine. Accessed October 6, 2022.

Hilderbrand, A., M. Zangrilli, M. Stinson. 2021. Decentralized clinical trial case study: five-stage process for recruiting and completing a site-less clinical study in less time and lower cost than traditional methods. *American Journal of Health Research* 9(6):213–217.

Horsey, D. What is a decentralized clinical trial (DCT)? *Medable.* Available at: https://www.medable.com/resource-center/what-is-a-decentralized-clinical-trial-dct. Accessed October 6, 2022.

Iacobucci G. 2022. Covid-19: NHS trusts declare "critical incidents" because of staff shortages. *The BMJ* https://doi.org/10.1136/bmj.o3.

Ilancheran, M. COVID-19's Impact of the clinical trial ancillary supplies industry. *Clinical Leader.* Available at: https://www.clinicalleader.com/doc/covid-s-impact-on-the-clinical-trial-ancillary-supplies-industry-0001. Accessed October 6, 2022.

Informa. 2021. Approaching data management complexity in decentralized and hybrid trials. Available at: https://scrip.pharmaintelligence.informa.com/-/media/marketing/scrip-asia-100/2022/jn4778-icon---data-management-article_final-10-2021_lr-(002).pdf? Accessed October 6, 2022.

IQVIA Institute. 2023. Global Trends in R&D 2022. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d2022. Accessed April 25, 2023.

Jhaveri, M., Lee, E. 2007. Performance of electronic diaries in diabetes clinical trials measured through overall satisfaction of site coordinators. *Journal of Diabetes Science and Technology* 1(4):522–30.

Johnson E. 2022.Trouble for trials—the worrying state of the research nurse workforce. *Contemporary Clinical Trials* 120:106878.

Khozin, S., A. Coravos. 2019. Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations. *Clinical Pharmacology & Therapeutics* 106:25–7.

Kelsey MD, Patrick-Lake B, Abdulai R, et al. 2022. Inclusion and diversity in clinical trials: actionable steps to drive lasting change. *Contemporary Clinical Trials.*116:106740.

Kim, J., K.A. Getz, C. Granville, et al. 2022. Measuring the impact of patient engagement capabilities: The development of the patient engagement capabilities questionnaire. Working Paper, Tufts CSDD.

Kozlov M. 2023. FDA to Require Diversity Plan for Clinical Trials. *Nature*. https://www.nature.com/articles/d41586-023-00469-4. Accessed May 1, 2023.

Kutzing, M., A. Deglincerti. Is a decentralized clinical trial right for your trial? & 5 tips for success. *Clinical Leader*. Available at: https://www.clinicalleader.com/doc/is-a-decentralized-clinical-trial-right-for-your-trial-tips-for-success-0001. Accessed November 2, 2022.

Lamberti, M.J., Z. Smith, A. Dirks, et al. 2022. The impact of decentralized and hybrid trials on sponsor and CRO collaborations. *Applied Clinical Trials.* Available at: https://www.appliedclinicaltrialsonline.com/view/the-impact-of-decentralized-and-hybrid-trials-on-sponsor-and-cro-collaborations. Accessed October 18, 2022.

Lasch, F., E-E. Psarelli, R. Herold, et al. 2022. The impact of COVID-19 on the initiation of clinical trials in Europe and the United States. *Clinical Pharmacology & Therapeutics* 111(5):1093-1102.

Le Breton, S., M. Lamberti, A. Dion et al. 2020. Covid-19 and its impact on the future of clinical trial execution. *Applied Clinical Trials*. Available at: https://www.appliedclinicaltrialsonline.com/view/covid-19-and-its-impact-on-the-future-of-clinical-trial-execution. Accessed December 29, 2022.

Liu J, Snipes R. Yes, Black patients do want to help with medical research – Here are ways to overcome the barriers that keep clinical trials from recruiting diverse populations. *The Conversation.* https://theconversation.com/yes-black-patientsdo-want-to-help-with-medical-research-here-are-

ways-to-overcome-the-barriers-that-keep-clinical-trials-from-recruiting-diverse-populations-185337. Accessed May 4, 2023.

Makri, A. 2019. Bridging the digital divide in health care. Lancet: Digital Health 1(5):e204–205.

Marquis-Gravel, G., M.T. Roe, M.P. Turakhia, et al. 2019. Technology-enabled clinical trials: transforming medical evidence generation. *Circulation* 140(17):1426–1436.

mdgroup. 2020. Why decentralisation is the future of clinical trials. Available at: https://mdgroup.com/blog/why-decentralisation-is-the-future-of-clinical-trials/. Accessed October 6, 2022.

Meadows, D.H. 2008. Thinking in systems: A primer. White River Junction, VT: Chelsea Green Publishing; p. 11.

Medable. 2020.The centricity of decentralizing: Breaking down the basics of decentralized clinical trials. Available at: https://www.centerwatch.com/whitepapers/medable/the-basics-of-decentralized-clinical-trials?white_paper_source=WPListing. Accessed October 6, 2022.

Medical Research Network. 2020. Decentralized clinical trials. Available at: https://www.clinicalleader.com/doc/decentralized-clinical-trials-how-to-deliver-the-complex-efficiently-0001. Accessed October 6, 2022.

McKenna, K.C., C. Geoghegan, T. Swezey, et al. 2021. Investigator experiences using mobile technologies in clinical research: Qualitative descriptive study. *JMIR Mhealth Uhealth* 19(2):e19242.

Miseta, E. 2021. Hybrid trials are impacting clinical research, but do patients want them? *Clinical Leader*. Available at: https://www.clinicalleader.com/doc/hybrid-trials-are-impacting-clinical-research-but-do-patients-want-them-0001. Accessed October 6, 2022.

Monat, J.P., T.F. Gannon. What is systems thinking? A review of selected literature plus recommendations. *American Journal of Systems Science* 4(1):11–26.

Parkins, K., A. Hillman. 2021. 2022 Forecast: Decentralised Trials to Reach New Heights with 28% Jump. *Clinical Trials Arena.* Available at: https://www.clinicaltrialsarena.com/analysis/2022-forecast-decentralised-trials-to-reach-new-heights-with-28-jump/. Accessed October 6, 2022.

Patil, R., C. Varner. 2020. Delivering clinical trial continuity during COVID-19. *IQVIA* Whitepaper. Available at: https://www.iqvia.com/library/white-papers/clinical-trial-continuity-during-covid-19. Accessed October 6, 2022.

Pennell N.A., C.M. Szczepanek, D. Spigel, et al. 2022. Impact of workforce challenges and funds flow on cancer clinical trial development and conduct. *American Society Clinical Oncology Education Book* 42:874–83.

Perry, B., C. Geoghegan, L. Lin et al. 2019. Patient preferences for using mobile technologies in Clinical trials. *Contemporary Clinical Trials Communications* doi.org/10.1016/j.conctc.2019.100399.

Posselt K. 2023. Reducing the Challenges Sites Face when Implementing Decentralized Trials. Pharma's Almanac. https://www.pharmasalmanac.com/articles/reducing-the-challenges-sitesface-when-implementing-decentralized-trials. Accessed April 25, 2023.

PPD Decentralized Clinical Trials Survey Report. 2020. Available at: https://www.ppd.com/wp-content/uploads/2021/03/PPD24_SurveyReport_Public_110220.pdf. Accessed December 29, 2022.

Price, J., N. Goodson, E.J. Warren, et al. 2021. Resilient design: Decentralized trials recovered faster from the impact of COVID-19 than traditional site-based designs. *Expert Review of Medical Devices18*(sup1):1–4.

Reites, J. 2020. Virtual visits: Moving clinical trials from clinics to homes. Innovation in clinical trial methodologies: Lessons learned during the Corona pandemic. p.61.

Riches, C. 2022. The digital future is now: making patient choice a reality. Available at: https://xtalks.com/webinars/the-digital-future-is-now-making-patient-choice-a-reality/. Accessed November 29, 2022.

Royal Academy of Engineering, Royal College of Physicians and The Academy of Medical Sciences. 2017. Engineering better care: A systems approach to health and care design and continuous improvement. Available at: https://raeng.org.uk/media/wwko2fs4/final-report-engineering-better-care-version-for-website.pdf. Accessed October 30, 2022.

Rubio-San Simón A., N. André, M. Cefalo, et al. 2020. Impact of COVID-19 in pediatric early-phase cancer clinical trials in Europe: a report from the Innovative Therapies for Children with Cancer (ITCC) Consortium. *European Journal of Cancer* 141:82–91.

Sarraju, A., C. Seninger, V. Parameswaran, et al. 2022. Pandemic-proof recruitment and engagement in a fully decentralized trial in atrial fibrillation patients (DeTAP). *npj Digital Medicine* 5(80).

Sather, S.S. 2018. Key considerations for the adoption of eConsent for sites. *Applied Clinical Trials.* Available at: https://www.appliedclinicaltrialsonline.com/view/key-considerations-adoption-econsent-sites. Accessed October 6, 2022.

Schneider, R.B., K.M. Biglan. 2017. The promise of telemedicine for chronic neurological disorders: The example of Parkinson's disease. Lancet Neurology 16(7):541–51.

Shikova, D. 2020. The benefits and barriers of decentralized clinical trials. TrialHub. Available at: https://trialhub.findmecure.com/blog/articles/the-benefits-and-barriers-of-decentralized-clinical-trials/. Accessed on October 6, 2022.

Sine, S., A. de Bruin, K. Getz. 2021. Patient engagement initiatives in clinical trials: Recent trends and implications. *Therapeutic Innovation & Regulatory Science* 55(5):1059-65.

Sommer, C., D. Zuccolin, V. Arnera, et al. 2018. Building clinical trials around patients: evaluation and comparison of decentralized and conventional site models in patients with low back pain. *Contemporary clinical trials communications* 11:120–26.

Sonnenberg, S.D. 2019. Developing a guide for patient centric logistics - get involved. ISPE. Available at: https://ispe.org/pharmaceutical-engineering/ispeak/developing-guide-patient-centric-logistics. Accessed October 6, 2022.

Spinner, J. 2021. Qualified mobile research nurses key to DCT success: Illingworth. *Outsourcing Pharma.* Available at: https://www.outsourcing-pharma.com/Article/2021/09/08/Qualified-mobile-research-nurses-key-to-DCT-success. Accessed October 6, 2022.

Stoecker, C. 2019. Virtual trial vs. personal touch: Is there a happy medium? *CenterWatch.* https://www.centerwatch.com/articles/12213-virtual-trial-vs-personal-touch-is-there-a-happy-medium. Accessed October 6, 2022.

Stunkel, L., C. Grady. 2011. More than the money: A review of the literature examining healthy volunteer motivations. *Contemporary Clinical Trials* 32(3): 342–52.

Tan, R.K., D. Wu, S. Day, et al. 2022. Digital approaches to enhancing community engagement in clinical trials. NPJ Digital 2022; 5(37):1–8.

Thoelke, K., G. Licholai. 2020. Decentralized clinical trials: The call for a new paradigm. *PRA Health Sciences White Paper*, Raleigh, NC. Accessed December 29, 2022.

Trebble, T. M., N. Hansi, T. Hydes, M.A. Smith, M. Baker. 2010. Process mapping the patient journey: An introduction. *The British Medical Journal* 341: 394–401.

Unger, J.M., R. Vaidya, D.L. Hershman et al. 2019. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *Journal of the National Cancer Institute* 111:245–55.

Van Norman, G.A. 2021. Decentralized clinical trials: The future of medical product development? JACC: *Basic to Translational Science* 6(4):384–7.

van Rijssel, T.I., A.J. de Jong, Y. Santa-Ana-Tellez, et al. 2022. Ethics review of decentralized clinical trials (DCTs): Results of a mock ethics review. *Drug Discovery* 27(10):103326.

WHO. 2023. Health Workforce. https://www.who.int/health-topics/health-sworkforce#tab=tab_1. Accessed Jan 5, 2023.

Xue, J.Z., K. Smietana, P. Poda, et al. 2020. Clinical trial recovery from COVID-19 disruption. *Nature Reviews Drug Discovery* 19:662–663.

Young, R. The digital future is now: making patient choice a reality. Available at: https://xtalks.com/webinars/the-digital-future-is-now-making-patient-choice-a-reality/. Accessed November 29, 2022.

Appendix

5.A A Discussion of the Advantages, Disadvantages, Obstacles, and Enablers Associated with DCTs

Perhaps the most significant advantage of DCTs is that they facilitate more accessible and convenient clinical trial participation. For study volunteers, this means less disruption to their daily lives, a convenient and flexible participation experience, and increased representation in clinical research. For sponsors, this results in better recruitment and retention and a larger and more diverse patient pool that offers the potential to complete trials faster and with increased external validity. For sites, DCTs can reduce staff workload and execution burden by allowing certain traditional site activities to be conducted remotely. Moreover, both sites and sponsors can benefit from the insights from real-time data collected in real-world settings. The efficiencies gained from DCTs carry the potential of significant cost advantages over time.

DCTs also pose certain disadvantages and must be implemented cautiously. Skepticism in the industry stemming from the capabilities and infrastructure that need to be built alongside the introduction of DCT solutions and the time and resources necessary before benefits are realized. For participants, DCTs require a more active role in the trial and data collection, which can be particularly challenging if participants' digital literacy falls short of what is needed, leading to potential inequalities. For sponsors, DCT implementation may necessitate new technology, new vendors (such as home HCPs), and new operational requirements. Sites and sponsors must make great efforts to maintain patient safety and to carefully consider how to ensure data protection, oversight, and data integrity.

Perhaps supply chain challenges most threaten DCT adoption given the changes required to facilitate drug logistics and management across multiple locations, including patients' homes. This necessitates a high degree of coordination across many stakeholders operating in different supply

chain areas and various geographies. Additionally, the number of nascent technology solutions and vendors has raised concerns regarding vendor selection and reliability, ease of integration, and interoperability of systems. Moreover, due to data in DCTs coming in from a wide range of sources, the complexity of data transfer, compilation, interpretation, analysis, and management has intensified. Such difficulties threaten the promise of DCTs and diminish their associated advantages. Considering and developing means to manage complexities is critical in overcoming obstacles to DCT uptake.

Despite the various challenges, many enablers continue to spur demand for DCT solutions. Although there have been calls for clearer guidelines, more recent articles indicate growing regulatory agency commitment for DCT use in clinical trials. Indeed, the COVID-19 pandemic has resulted in increased and quickly evolving regulatory acceptance of decentralized interventions. Furthermore, the pandemic has helped improve attitudes toward digital health solutions and has heightened stakeholder comfort levels with digital technologies. These shifts in attitudes, alongside digital advances, growing sponsor and CRO investments to developing and bolstering IT infrastructure, and efforts to simplify protocol designs, will undoubtedly reinforce the continued adoption of DCTs.

Advantages

Better recruitment and retention: Currently, 85% of traditional clinical trials fail to recruit enough patients, and 80% are delayed due to recruitment problems (Clinical Leader 2012). Challenges with recruitment and retention can be incredibly costly for the sponsor, with direct and indirect costs reaching as high as $8 million per day (Hargreaves 2016). Conventional trials may cause significant disruption to participants' everyday lives. In a recent study, more than 12,000 respondents patient travel was identified as the top burden to participation, “with 3 of 10 (29%) indicating that it was “somewhat” or “very burdensome” (Sine et al. 2021). DCTs enable a greater recruitment and retention rate by allowing trial activities to occur outside sites (Sommer et al. 2018). They have shown promise, particularly during the COVID-19 pandemic. For example, a recent study found that DCT supported clinical trials were the only ones that recovered and

exceeded pre-COVID recruitment rates compared to traditional clinical trials, which never fully recovered (Price et al. 2021).

Enhanced access: In conventional trials, sites tend to be located in urban areas (Galsky et al. 2015). The lack of availability of local trials serves as a barrier to participation for patients living in rural areas (Unger et al. 2019, Schneider and Biglan 2017). DCTs allow more patients to have access to innovative medicines (Sommer et al. 2018). Moreover, with a larger patient pool, sponsors can benefit from a faster recruitment rate (Horsey 2022).

Increased diversity: Relatedly, another area that can most certainly benefit from a DCT approach and the increased accessibility that it enables is patient diversity. As different patient subgroups may respond differently to therapies, the lack of diversity in clinical trials may mean that findings from a largely homogenous participant pool may not be generalizable (Clark et al. 2019). Despite the need to include patients representing the general population, less than 5% of eligible patients participate in clinical research, and the figure is even smaller for racial and ethnic minorities, who are continually underrepresented in clinical research (Goodson et al. 2022). As previously discussed, the traditional site-centric archetype severely limits the participation of such individuals unable to travel for study visits. Such obstacles inadvertently lead to the exclusion of patient populations from underserved geographic areas. Though DCTs cannot solve all the barriers mentioned, they can mitigate some of the major challenges related to accessibility, the most obvious being DCTs' ability to make certain clinical research studies more geographically accessible compared to traditional studies. By increasing accessibility and removing some of the financial toxicities of clinical trial participation (Khozin and Coravos 2019), DCTs could lead to better representation and increase the external validity of trial findings (Marquis-Gravel et al. 2019).

Improved patient engagement: DCTs can also positively influence patient engagement - the effort and movement to amplify and address patient voices in drug development and delivery. The flexibility afforded by DCTs can enrich the patient experience (ACRO 2020). A convenient trial experience can make it easier for patients to participate and remain in the trial, thereby increasing

compliance and adherence (Sommer et al. 2018), which may enhance study safety (Van Norman 2021).

RWD & RWE: Electronic data capture gives sites and sponsors real-time access to data, which has multiple benefits. Issues can be quickly identified and addressed (ACRO 2020). For instance, sites can be altered to safety problems between on-site visits (Reites 2021). By reviewing data more quickly, sponsors can derive insights to optimize study outcomes (Informa 2021) and use data to inform clinical trial design. Data collected in real-world settings while a participant goes about their daily routines may represent the patient's experience more than data obtained through discrete site visits (Coran et al. 2019).

Reduction in site burden: DCTs allow certain traditional site activities, such as drug administration and assessments, to be conducted remotely by participants or other HCPs, reducing site investigators' workload (Van Norman 2021). As a result, site investigators become free to pursue more complicated, high-value services (Spinner 2021). The efficiency and resources gained can reduce the number of sites needed to meet recruitment targets for a study (Sommer et al. 2018) and expand the number of trials that can be carried out simultaneously (Medable 2020).

Cost advantages: With DCTs, fewer research sites may be needed, and this could potentially reduce the number of institutional review boards and redundant applications. As a result, costs and site-specific inconsistencies might decrease while making it easier to implement protocol adjustments (Van Norman, 2021). Moreover, the remote collection of digital biomarkers could facilitate a reduction in trial sample sizes (Khozin and Coravos 2019).

Disadvantages

Industry aversion: According to Agrawal et al. 2021, across sponsors, there can exist “skepticism about the urgency of adopting [DCT] approaches, internal cost pressures, lack of an established operating model for decentralization, and an increased amount of capability that must be built across asset teams, functions, digital and technology groups, and vendor management, among

others". DCTs can also be burdensome to sites, particularly in the early stages of implementation. Lamberti et al. 2022 found that many organizations are experiencing barriers related to effectively using DCT technologies such as ePRO and eConsent. Moreover, the digital tools meant to simplify the process may burden the sites. For example, a recent report revealed that the average site must log into more than six platforms for a single study (Florence Healthcare 2022b), making the process cumbersome for the end user. Both studies underscore pain points related to identifying and using the right technology and highlight the importance of making it easy for end users to effectively and seamlessly use the different technologies.

Potential inequalities: DCTs may introduce or exacerbate inequalities by excluding populations who do not have access to communication devices or the internet (Tan et al. 2022). Only 45% of people have internet access in developing countries, with just 20% in the least developed countries (Makri 2019). The percentage of those connected in rural areas is three times lower than in urban areas (Makri 2019). In the US, 20% of the population does not have access to broadband or a smartphone (Goodson et al. 2022). Moreover, participants from low-income groups might not have private spaces to discuss confidential topics with clinical investigators (Kelsey et al. 2022). van Rijssel et al. (2022) also highlight concerns about digital literacy as a potential participation barrier, as DCTs would require patients to have a certain level of digital literacy to work with the different technological platforms. Thus, providing high-quality support through training to increase participants' comfort and willingness to use technology will be paramount to ensuring the successful implementation of DCTs.

Privacy & data protection: It is important to maintain patient confidentiality and protect health data according to laws and regulations (such as GDPR or HIPPA), which may vary from country to country. This is so that data emerging from DCT elements, such as wearables, is not misused (e.g., potential discrimination from insurers based on cardiac activity recorded on a smartwatch) or hacked (Goodson et al. 2022).

Patient acceptance: DCTs place a hefty burden on the patient. For instance, van Rijssel et al. (2022) pointed out that DCTs rely heavily on patients to monitor and report relevant data compared to traditional clinical trials where this is done at sites. Moreover, participants differ in their desire

for human interaction, which may cause a preference for in-person visits. The relationship with study staff can be critical, especially when a participant is enrolled in a clinical trial for the first time (Shikova 2020). As respondents to a patient insight survey indicated, these relationships appear to contribute to a positive experience even when the therapeutic offered no benefit to them (Miseta 2021). Since one of the main benefits of trial participation is attention from experts, virtual trials may be too impersonal (Stoecker 2019).

Operational requirements: One concern with DCTs is that home care staff and patients play a more active role in trial and data collection and may not be able to provide the same level of oversight and environmental control as a principal investigator at an approved study site (ArcheMedX 2022), which may lead to faulty data and flawed conclusions (Banks 2021). This has also sparked concerns regarding accountability from competent authorities since even though a home healthcare provider (which is not typically hired by the investigator) may be seeing patients, the investigator retains ultimate responsibility for the care given (Posselt 2023) and the data obtained. This raises the question of whether investigators are willing to delegate responsibilities to vendor staff particularly when it relates to primary and secondary endpoints. To ensure tasks can be shifted away from on-site investigators, it is imperative to provide support and training to the clinical research staff. A recent study showed that the level of training received by clinical research staff to interact with patients meaningfully was generally lacking (Kim et al. 2022), illustrating an area that organizations may want to pay more attention to, particularly as it relates to DCTs. Having a well-trained staff that understands how to help patients stay connected and engaged while providing accurate biometrics will no doubt be integral to ensuring the continued implementation of DCTs. Other risks to data integrity may stem from the fact that home nurses need to work with the equipment on hand. Technological failures may result in data loss without an expert to provide immediate fixes (mdgroup 2020). Moreover, with nurses taking patient samples to local laboratories for processing rather than having one central laboratory, data-transfer issues, and potential variance in data standards across multiple laboratories might jeopardize data consistency (Informa 2021). Although samples can still be sent to a central laboratory if suppliers and shipping material are provided to home HCP, this may introduce different challenges such as longer delivery times and higher transportation costs.

Obstacles

Increased supply chain complexity: A major complexity of DCTs is drug logistics and management. Unlike conventional trials, where drugs are shipped to centrally managed centers, DCTs require shipment to multiple coordinating locations (including patients' homes) (Van Norman 2021). Drugs need to be delivered in good quality and at the right time (often to coincide with a visit from an HCP), which necessitates substantial coordination among the supply chain, including logistics and technology providers, HCPs, and patients (Applied Clinical Trials 2022). Issues in coordination can jeopardize the promise of DCTs. For instance, certain trial durations increased in the decentralized arm compared to the conventional setting in one study, mainly because some patients took several days to retrieve drug shipments from their local post office (Sommer et al. 2018). One advantage of DCTs is increased access (e.g., to participants living in rural areas). However, this complicates logistics as there are varying levels of infrastructure across geographies. Adding to the complexity, in global studies, IMP and other clinical trial materials must be packaged, stored, and transported to comply with the regulations in each country the shipment passes through (Applied Clinical Trials 2022).

IT Infrastructure: Another complexity arises from the need for new IT infrastructure. Organizations may have concerns about the cost, time, effort, and training required to acquire and implement new technology. Clinical researchers often have busy schedules and limited time to learn new software (Florence Healthcare 2022). Vendor management also creates difficulties. For instance, there is an abundance of vendors. As stated by one industry professional, there are “15 different possible vendors for every single activity or step that goes into running a clinical trial”, creating a “tsunami effect” and complicating vendor selection (Halloran 2020). Choosing a vendor with less experience with clinical trials can create challenges for data reliability (Informa 2021). Since data is amalgamated centrally from multiple healthcare providers using multiple health record systems, there is also a concern regarding the interoperability and ease of integration of IT systems (Van Norman 2021).

Data management: There are also complexities around data management stemming from the range and heterogeneity of data sources in DCTs (Informa 2021). The use of multiple parties in various sites with possibly different interfaces increases the security risk of a systems breach by external actors (ACRO 2020). Establishing cybersecurity capabilities for executing DCTs (Khozin and Coravos 2019) and ownership, accountability, and oversight of data are critical to ensuring data security (Coran et al. 2019). Lastly, the range and volume of data can complicate the utilization and data management for staff. DCTs can be more complicated and time-consuming than conventional trials if staff must spend hours sifting through data and transferring data across various systems (Florence Healthcare 2022).

Staff Shortages: The world's population has been growing and aging and there has been a rising burden of chronic disease (Betcheva et al. 2020). At the same time, the healthcare workforce is also aging with a large portion set to retire. The WHO estimate a projected global shortfall of 10 million health workers by 2030 (WHO 2023). The COVID-19 pandemic exacerbated staffing problems among healthcare professionals. For instance, due to staff absences jeopardizing their ability to keep services running, some NHS trusts in England declared "critical incidents" (Iacobucci 2022). Staffing issues also impacted clinical research. Staff constraints resulted in challenges with site initiation, monitoring activity, patient recruitment, and patient care (Rubio-San Simón et al. 2020). There are also lingering consequences from the pandemic. With staff working remotely or in a hybrid fashion, there has been a loss of side-by-side learning with experienced staff and a limitation in cross-coverage, both of which have negatively impacted staff recruitment and onboarding (Pennell et al. 2022). Moreover, COVID-19 caused attrition in clinical personnel. Attrition issues are attributed to "burn out… increasing clinical trial complexity, morale, lack of support (due to staff shortages) …lack of experience of new hires", among others (Dizon et al. 2022). Furthermore, with the rapid rollout of decentralized trials, there have been reports of stress and anxiety related to the digital delivery of trials among research nurses (Pennell et al. 2022). Exacerbating the problem is the fact that training has not been widespread nor tailored creating gaps in the organizational support offered to nurses conducting remote or hybrid trails (Pennell et al. 2022). With historically high clinical trial activity and increased utilization of decentralized trial models (IQVIA Institute 2023), the need for adequate staffing of experienced research professionals such as clinical research nurses is paramount (Johnson 2022).

Decentralization (especially for disease areas such as cancer) increases demand for research nurses that have strong participant management skills to support trial designs which incorporate digital health (e.g., safety monitoring and remote data capture through wearables) (Johnson 2022). However, with rising numbers of nurses leaving the workforce or retiring, and long lead times to train new personnel, some have raised concerns whether staff can facilitate the development of novel therapies through decentralized models (Johnson 2022).

Enablers

Regulatory guidance & changes: To minimize disruption to ongoing trials and clinical research during the COVID-19 pandemic, regulators such as the FDA and EMA issued guidance permitting the integration of alternative trial elements. Methods included virtual visits, remote monitoring, and self-administration of doses (FDA 2021, EMA 2020). With increased regulatory acceptance, further guidance across different countries will likely evolve (Agrawal et al. 2021). Notable developments for the DCT industry include the FDA's launch of the Digital Health Center of Excellence, which "marks the beginning of a comprehensive approach to digital health technology, setting the stage for advancing and realizing the potential of digital health" (FDA 2022) as well as the formation of the Decentralized Trials and Research Alliance that brings together sponsors, CROs, patient advocacy groups alongside the FDA, to promote the widespread adoption of decentralized research methods (DTRA 2021).

Protocol simplification: Studies have found that protocol design complexity has grown rapidly (Getz and Campo 2018), having detrimental implications for investigative site burden, patient burden, and clinical trial performance (e.g., longer cycle times and higher costs) (Getz et al. 2019). Excessive data collection associated with complex protocol designs can compromise the data analysis process, increase error rates, and negatively impact data quality (Getz 2014). The shutdowns brought about by the COVID-19 pandemic provided a catalyst for streamlining study procedures to focus on what was absolutely necessary (Halloran 2020). Concurrently, traditional site-based designs were retrofitted to allow for decentralization. As DCT adoption continues to grow, studies must be optimally designed upfront for decentralization (Spinner 2021).

Digital advances & funding interest: There is considerable investor interest in digital health, with venture capital funding for digital health technologies exceeding investments made on all medical devices combined (Marquis-Gravel et al. 2019). Technology companies, including Big Tech firms like Apple and Amazon, have moved into the healthcare market. According to Grand View Research, increasing smartphone penetration, improving internet connectivity, and advancing healthcare IT infrastructure, among other factors, are driving growth in the global digital health market (valued at USD 175.6 billion in 2021 and projected to grow at a compound annual growth rate of 27.7% by 2030 (Grand View Research 2022)). What is more, technologies for remote data collection are maturing and increasingly being validated, with more digital endpoints used as primary endpoints (Agrawal et al. 2021).

Comfort with digital health: Following the COVID-19 pandemic, attitudes towards digital health have improved both on the consumer and provider side. According to research by McKinsey, telehealth utilization in 2021 is 38X higher than before the pandemic. The analysis also shows that 58% of physicians continue to view telehealth more favorably now than they did before COVID-19, and 40% of consumers believe they will continue to use telehealth compared to just 11% using telehealth prior to the pandemic (Bestsennyy et al. 20210. Comfort with digital technologies has also grown. A 2020 survey of healthcare consumers by Deloitte indicates that 42% of U.S. consumers used tools to measure and track their fitness and health (jumping from 17% in 2013). Among those using a fitness device, half shared data obtained from the technology with their doctor (Betts et al. 2020).

Chapter 6

Conclusion

The dissertation studies the major challenges and complexities in managing healthcare ecosystems. The research strives to better understand and critically evaluate problems through the utilization of operations management strategies and methodologies with the aim of offering actionable insights for key decision–makers and healthcare practitioners.

The essays in the dissertation follow an overarching "systems thinking" approach to address different problems. The broader healthcare system includes all the entities involved in the provision of medical products and services and is comprised of various subsystems, each wide ranging in both their functions and roles. There are many interacting elements within and across healthcare systems. Although elements can be people, processes, information, organizations, and services (Royal Academy of Engineering et al. 2017), each of the dissertation's core chapters mainly focuses on the interactions between key stakeholders and studies how stakeholder decisions invariably impact other areas of the system. Supply chain management is a management strategy that is characterized by a systems approach in that it considers the organizations in a supply chain as an end–to–end integrated entity (Mentzer et al. 2001). With a focus on healthcare delivery, the initial half of the dissertation demonstrates the relevance and applicability of supply chain management in healthcare, whilst the second half of the dissertation examines how recent developments in pharmaceutical systems (the changing nature of outsourcing relationships and trial decentralization) have affected stakeholder interactions in clinical development.

Chapter 2 of the dissertation delineates and categorizes healthcare supply chains into four main categories and eleven subcategories. The chapter considers the key stakeholders for each category and the main challenges and risks they face. The essay also discusses the existing academic research and puts forward at least one effective and efficient supply chain strategy that has been employed in practice pertaining to each category. The research serves two main purposes for industry and the academic community. First, by categorizing healthcare supply chains and

outlining the pressing issues burdening each category, the essay lays the groundwork for further involvement of supply chain management scholars in the healthcare domain. Second, by demonstrating the applicability and value of supply chain management in healthcare, the essay advocates for more supply chain management research by academics working in healthcare operations and for the increased adoption of supply chain management concepts, tools, and strategies by healthcare practitioners.

Chapter 2 offers an organized view of the healthcare ecosystem and its subsystems and calls attention to the research potential in healthcare supply chain management. Building on the learnings from Chapter 2, Chapter 3 addresses this call by illustrating how supply chain management concepts and strategies can be applied and tailored to healthcare through a careful consideration of the system's unique challenges and opportunities. Focusing on the practical relevance of research, the essay offers readers a way to systematically think about addressing healthcare challenges from a supply chain perspective. This is achieved by following a framework that is customer focused, systems based and strategically orientated and that *simultaneously* considers clinical, operational, and financial dimensions. Exemplifying the framework, the chapter considers several supply chain strategies (such as coordination, integration, and incentive mechanisms, to name a few) in healthcare supply chains that are either commonly used in or have a high potential to be applied to healthcare. The chapter also highlights notable developments that shift care from treatment to prevention, from hospitals and clinics to primary care and patients' homes, and from broad treatment approaches to personalized/precision medicine. These trends alter healthcare supply chains and demand a redesign of current systems. Applying the framework, the chapter considers how new care models shape healthcare supply chains of the future.

While still focused on stakeholder interactions, the latter half of the dissertation shifts attention from healthcare delivery to the pharmaceutical industry, and in particular, to clinical development. Chapter 4 explores pharmaceutical outsourcing relationships between a pharmaceutical company and its provider, a CRO. The essay investigates if and how a pharmaceutical manager's choice of outsourcing relationship can affect clinical trial timelines. The problem is formulated as a three–stage game between the two parties and considers two relationship types; a strategic partnership (characterized by a pharmaceutical company's commitment of future business to the CRO) and a

transactional arrangement (a one–off but potentially repeated engagement). By characterizing the conditions under which either type of relationship should be pursued, several insights with managerial implications are derived. It is shown that although more environments are conducive to strategic partnerships than not, there is still a place for transactional arrangements (such as when the benefits from commitment are limited). The chapter also demonstrates the importance of the relationship's operational details. The analysis shows that a strategic partnership with a well–structured termination strategy enables incentive alignment between the pharmaceutical company and CRO devoid of high payments and high fines borne by either party. To the best our knowledge, the relationships between pharmaceutical companies and CROs have not yet been explored by operations scholars. By evaluating the role of transparency and commitment in such partnerships, the work builds on and contributes to operations management literature on project management, performance–based contracting, pharmaceutical contracting, and clinical trial operations.

By examining the impact outsourcing relationships on clinical trial duration, Chapter 4 studies operational decisions that can improve the efficiency of clinical trials. With a similar focus on clinical trials, Chapter 5 explores how the adoption of trial decentralization alters the clinical development landscape. DCTs can mitigate many existing challenges in clinical development such as patient and provider burden, patient recruitment and retention issues, access, the timeliness and quality of data, among others, thereby potentially enhancing trial efficiency. However, DCT deployment introduces new demands and pressures onto existing systems that can diminish its promise and ease of implementation. As the prominence of DCTs grows and more is learned about the positives and negatives of DCTs, it is becoming increasingly important that stakeholders can adequately weigh the benefits and risks of adopting decentralized approaches into current systems. Employing systems thinking, the essay proposes a conceptual framework to evaluate the impact of DCT deployment on key stakeholders (patients, pharmaceutical sponsors, and investigative sites) through a reiterative assessment of pain points. By outlining the process of emergence and alleviation of stakeholder pain points, the essay offers a systematic way of uncovering and addressing implementation challenges, carrying practical managerial implications for various decision–makers involved in clinical development.

The essays forming Chapters 2 and 3 of the dissertation have been published. Through the categorization of healthcare supply chains and the conceptualization of a supply chain thinking framework in healthcare, it is hoped that the work spurs further interest and future research in supply chain management in the healthcare domain. For instance, the essays provide a high–level overview of how supply chain management can be applied and tailored to the broader healthcare ecosystem. Research narrowing in on particular healthcare supply chains and their challenges may lead to opportunities to adapt frameworks and learnings from other domains for the healthcare context, and to develop new research to advance healthcare supply chain management.

The essay forming Chapter 4 of the dissertation is still a work in progress and a note on its limitations is merited. The work has undergone a first round of peer review. The revision of the research will address issues raised by external reviewers–here I will discuss two main concerns. First, the modelling of the problem focuses on the actions that the pharmaceutical company can take to decrease clinical trial duration (relating to transparency and commitment) that are within the company's control. Thus, for the sake of simplicity, a deterministic duration for the two projects was assumed. However, we acknowledge that this is not necessarily reflective of reality and in practice there may be considerable uncertainty stemming from external shocks. Second, a deliberate choice was made not to endogenize the contract parameters. This was done in an effort to examine the different environments, characterized by *various parameter sets*, under which a pharmaceutical company will choose either type of relationship. However, endogenizing the contracts would more closely align the research with practice and allow for the determination of optimal terms, possibly leading to different and interesting insights.

The essay forming Chapter 5 has been published. The research provides a framework to assess the emergence and alleviation of pain points through DCT implementation. A natural next step for future research would be to evaluate the impact of introducing DCT elements into systems by empirically quantifying the value generated for different stakeholders. Comparative studies between conventional, hybrid and virtual trials exploring a range of outcomes (e.g., patient engagement, access and diversity, time, costs, data quality, etc.) may generate valuable insights regarding the use and applicability of DCTs in different systems and could lead to the development

of scoring tools to systematically apply DCT elements and solutions to clinical trials for various conditions.

In conclusion, the dissertation aims to demonstrate that in order to wade through the difficulties in managing healthcare ecosystems, complicated and often inefficient systems, one needs to carefully consider the many interacting elements that comprise the system. Through the utilization of operations management concepts, strategies, and methodologies, the dissertation provides several essays that evaluate and address major healthcare challenges from a system's perspective.