Contextualising technology and practice adoption in healthcare settings

Sandra Gillner

geboren in Starnberg, Deutschland

Inauguraldissertation zur Erlangung der Würde eines

DOCTOR ADMINISTRATIONIS REI PUBLICAE

der Wirtschafts- und Sozialwissenschaftlichen Fakultät

der Universität Bern

betreut von

Prof. Dr. Rudolf Blankart

KPM Center for Public Management

Universität Bern

21 June 2024

Sie dürfen:

Teilen — das Material in jedwedem Format oder Medium vervielfältigen und weiterverbreiten

Der Lizenzgeber kann diese Freiheiten nicht widerrufen solange Sie sich an die Lizenzbedingungen halten.

Unter folgenden Bedingungen:

Namensnennung — Sie müssen angemessene Urheber- und Rechteangaben machen , einen Link zur Lizenz beifügen und angeben, ob Änderungen vorgenommen wurden. Diese Angaben dürfen in jeder angemessenen Art und Weise gemacht werden, allerdings nicht so, dass der Eindruck entsteht, der Lizenzgeber unterstütze gerade Sie oder Ihre Nutzung besonders.

Nicht kommerziell — Sie dürfen das Material nicht für kommerzielle Zwecke nutzen.

Keine Bearbeitungen — Wenn Sie das Material remixen, verändern oder darauf anderweitig direkt aufbauen , dürfen Sie die bearbeitete Fassung des Materials nicht verbreiten.

Keine weiteren Einschränkungen — Sie dürfen keine zusätzlichen Klauseln oder technische Verfahren einsetzen, die anderen rechtlich irgendetwas untersagen, was die Lizenz erlaubt.

Hinweise:

Sie müssen sich nicht an diese Lizenz halten hinsichtlich solcher Teile des Materials, die gemeinfrei sind, oder soweit Ihre Nutzungshandlungen durch Ausnahmen und Schranken des Urheberrechts gedeckt sind.

Es werden keine Garantien gegeben und auch keine Gewähr geleistet. Die Lizenz verschafft Ihnen möglicherweise nicht alle Erlaubnisse, die Sie für die jeweilige Nutzung brauchen. Es können beispielsweise andere Rechte wie Persönlichkeits- und Datenschutzrechte zu beachten sein, die Ihre Nutzung des Materials entsprechend beschränken.

University of Bern
KPM Center for Public Management
Freiburgstrasse 3
3010 Bern
Switzerland

www.kpm.unibe.ch

b
UNIVERSITÄT
BERN

KPM
KOMPETENZZENTRUM
PUBLIC MANAGEMENT

Die Fakultät hat diese Arbeit am 22. August 2024 auf Antrag der beiden Gutachter Prof. Dr. Blankart und Prof. Dr. Winter als Dissertation angenommen, ohne damit zu den darin ausgesprochenen Auslassungen Stellung nehmen zu wollen.

Acknowledgements

Reflecting on my past three years at the University of Bern, I want to express my gratitude to those who supported me along the way. My sincere thanks go to my supervisor Rudolf Blankart, whose support in the past three years granted me a valuable chance to grow with my challenges and freely shape my academic journey. He has been a reliable and trusted source of advice and guidance, and I immensely enjoyed working in his team and by his side. I am grateful that my workplace at the juncture of the KPM and sitem-insel was a place of collegiality and shared laughter – I particularly thank Kosta, Lize, Alissa, JP, Benjamin, and Rachel, all of whom shared this journey and never hesitated to celebrate my successes with me.

I had the privilege to gain access to an inspiring scientific community: I thank my co-authors listed in this thesis for the opportunity to learn by their side and for being excellent sparring partners. Thank you to the Screen4Care project consortium for creating an ambitious and challenging environment for this thesis. Thank you to the Harvard-MIT Center for Regulatory Science for welcoming me with open arms in Boston and granting me a unique chance at broadening my academic horizons.

I have been extremely lucky to be part of a wider support system outside of the University, which has shown the utmost patience, love, and genuine interest in this project – thank you, Layla, Ines, and Karin.

I dedicate this dissertation to the people who shape how I think about the world: To my father, Frank, and my mother, Gabi, who gave me a childhood that instilled in me confidence in myself and curiosity about the world, empowering me to take on this endeavour. To my sister Katrin, who inspires and encourages me to become the best version of myself. To Dado – you have shared every burst of 'growing pains' and excitement of this doctoral journey with me and have shown nothing but unwavering belief in me. I truly cannot wait to embark on the next adventure knowing you are by my side.

Bern, June 2024 *Sandra Gillner*

Contents

List of Figures

List of Tables

Introductory remarks

This cumulative doctoral dissertation analyses the role of context for the adoption of new technology and practices in healthcare settings. Throughout the three included papers, my research explores why the introduction of a novel technology or practice may succeed in one environment or context while it fails in another. Context can be described as the changing "situational opportunities and constraints" (Johns, 2006) that affect adoption processes and their outcomes.

These situational opportunities and constraints can present themselves at multiple levels and across different dimensions of the healthcare system (Hitt et al., 2007). The papers included in this work therefore take a multi-faceted approach to decipher and explore such opportunities and constraints, considering both organisational as well as systemic perspectives. Beyond offering a micro-level management perspective on healthcare institutions (paper 2), my research also contributes to macro-level policy relevant insights, which span entire healthcare systems (paper 1 & 3).

To explore context in its diversity, my co-authors and I employ a range of qualitative and quantitative research methods. Qualitative research, including the analysis of semi-structured interviews and surveys (papers 1-2), lends itself to offer an in-depth account of the rich nuances of context, whereas quantitative research (paper 3) helps to synthesise contextual complexities to enhance our ability to compare different contexts. Both methodological approaches have their merits and are therefore used jointly in this dissertation.

The intent of this dissertation is to contribute relevant and actionable insights to contemporary debates on how to achieve technology and practice adoption across variable contexts in healthcare management. At the time of writing, these contemporary debates revolve around advances of artificial intelligence and gene-based technologies, which exploit our growing knowledge of human DNA for better disease prediction and treatment. Additionally, new practices for improving the quality of care in hospitals are continuously developed and introduced to healthcare systems,

owing to the growing calls for better quality of healthcare service delivery (Auerbach, Landefeld & Shojania, 2007).

In paper 1, I examine the introduction of artificial intelligence-based diagnostics in complex healthcare systems. Complex systems theory is employed to capture the multidimensional nature and contingency of context for any actor and process situated in such systems. Semi-structured interviews with AI providers were used to investigate this area of research, whose role in perpetuating AI use in healthcare has previously been understudied; AI providers were found to have developed unique properties to better adapt to variable and unpredictable complex healthcare contexts. My results illustrate the role of stealth science, agility, and digital ambidexterity for AI providers to overcome the perceived challenges of operating across organisational boundaries and contexts when spreading AI in healthcare systems.

Paper 2 reveals how a centrally coordinated quality improvement programme involving multiple German hospitals fails at ensuring the homogenous implementation of quality improvement measures across participating organisations. Its main theoretical contribution lies in the use of a social network approach to understand why some organisations progress further in their attempts of implementing quality improvement measures than other members of the collective. Drawing on interviews and survey data, this study highlights the role of relational context within healthcare organisations – measured via the structure of social networks – as a contextual factor impacting adoption progress.

Finally, paper 3 offers a quantitative analysis of how submissions of marketing authorization applications for gene and cell therapies compare between two regulatory agencies in terms of timing and reporting of clinical trial data. We analyse concordance of the evidence reported to the U.S. Food and Drugs Authority (FDA) and the European Medicines Agency (EMA) via descriptive statistics to show how drug sponsors present clinical evidence differently depending on the evaluating agency and timing of submission of their application. This study thus contributes to our knowledge about the role of regulatory context in ensuring access to safe and efficient medicines.

In its entirety, this thesis sheds new light on the role of context for the adoption of selected new technologies and practices in healthcare: Context not only directly restricts or enables technology and practice adoption, but it also carries meaning for actors within the healthcare system. By making sense of a new technology or practice and interpreting its implications for a given context, actors adapt their own behaviours. These processes of sensemaking and interpretation affect the adoption trajectories in each context and can be observed throughout all three papers included in this thesis: Technology developers anticipating negative feedback from prospective users and consequently adopting unique properties; Quality improvement managers seeking to identify allies within their own organisation who would support a new initiative; And drug sponsors strategizing around expected regulatory rigour when introducing their product to different markets. Healthcare managers and other decisionmakers may recognise that overcoming contextual barriers to technology and practice adoption requires an assessment of the expectations and incentives created for a new technology within each context, as these are consequential for its adoption to succeed and, ultimately, for realising improvements in patients' health.

Bibliography

Johns G. 2006. The essential impact of context on organisational behaviour. *Academy of Management Review, 31*(2)*:* 386-408. DOI: 10.5465/amr.2006.20208687

Hitt M. A., Beamish P. W., Jackson S. E., & Mathieu J. E. 2007. Building theoretical and empirical bridges across levels: Multilevel research in management. *Academy of Management Journal, 50*(6): 1385-1399. DOI: 10.5465/amj.2007.28166219

Auerbach A. D., Landefeld S. & Shojania K. G. 2007. The Tension between Needing to Improve Care and Knowing How to Do It. *The New England Journal of Medicine, 357*(6): 608–613. DOI: 10.1056/NEJMsb070738

Paper 1

We're implementing AI now, so why not ask us what to do? – How AI providers perceive and navigate the spread of diagnostic AI in complex healthcare systems

---

Citation: Gillner, S. 2024. We're implementing AI now, so why not ask us what to do? – How AI providers perceive and navigate the spread of diagnostic AI in complex healthcare systems. *Social Science and Medicine 340*. DOI: 10.1016/j.socscimed.2023.116442

Acknowledgements and funding: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101034427. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This study was conducted as part of the Screen4Care project and has received valuable feedback during its early conception by individual beneficiaries: Kosta Shatrov, Anne-Sophie Chalandon, Alicia Granados, Rumen Stefanov, Georgi Stefanov, Georgi Iskrov, Ralitsa Raycheva, Gulcin Gumus, Edith Gross, Andreas Clemens, and Julian Nam. Special thanks go to Carl Rudolf Blankart for his critical review of the manuscript. A preliminary working version of this paper was presented at the Academy of Management 2023 Annual Meeting in Boston, US, and the European Forum for Studies of Policies for Research and Innovation 2023 in Brighton, UK.

Abstract

Despite high expectations of artificial intelligence (AI) in medical diagnostics, predictions of its extensive and rapid adoption have so far not been matched by reality. AI providers seeking to promote and perpetuate the use of this technology are faced with the complex reality of embedding AI-enabled diagnostics across variable implementation contexts. In this study, we draw upon a complexity science approach and qualitative methodology to understand how AI providers perceive and navigate the spread of AI in complex healthcare systems. Using semi-structured, one-to-one interviews, we collected qualitative data from 14 providers of AI-enabled diagnostics. We triangulated the data by complementing the interviews with multiple sources, including a focus group of physicians with experience using these technologies. The notion of embedding allowed us to connect local implementation efforts with systemic diffusion. Our study reveals that AI providers self-organise to increase their adaptability when navigating the variable conditions and unpredictability of complex healthcare contexts. In addition to the tensions perceived by AI providers within the sociocultural, technological, and institutional subsystems of healthcare, we illustrate the practices emerging among them to mitigate these tensions: stealth science, agility, and digital ambidexterity. Our study contributes to the growing body of literature on the spread of AI in healthcare by capturing the view of technology providers and adding a new theoretical perspective through the lens of complexity science.

Introduction

The widespread deployment of information technology in healthcare systems has generated a vast amount of health data. This data abundance, along with increased computational power, has sparked a growing interest in harnessing the clinical and financial value of pooled patient information through artificial intelligence (Shaw et al., 2019; Chen, Chiang & Storey, 2012). Artificial intelligence (AI) can be defined as the emulation of cognitive human behaviour by machines to automate the tasks of identifying and solving complex problems (Åström, Reim & Parida, 2022, Lee et al., 2019). Many AI applications are being used to improve and extend the performance of existing electronic clinical decision-support tools, which have long aimed to standardise and improve decision-making in medicine (Sutton et al., 2020). One expanding use case of AI in healthcare is the (pre-)diagnosis of diseases, particularly those that are rare and difficult to diagnose. AI-enabled clinical diagnostic tools are widely seen as the most promising applications of AI in healthcare due to their potential to increase the accuracy and timeliness of medical diagnoses (Berente, Gu & Recker, 2021). It is therefore unsurprising that a wave of new stakeholders has recently entered healthcare systems seeking to commercialise the technology (Zahlan, Ranjan & Hayes, 2023).

AI providers have been keen to exploit the optimism around AI technologies and promote the spread of AI across healthcare systems (Garbuio & Lin, 2019). However, while local initiatives to implement AI-enabled diagnostic tools have proliferated in recent years, predictions of the extent and rapidity of their spread have so far not been matched by reality. Indeed, there are numerous reports of organisations abandoning or failing to implement such tools (Raji et al., 2022; Sun & Medaglia, 2019). AI providers are thus confronted with the paradox of 'pilotitis', where an abundance of AI pilot projects are initiated but fail to be replicated elsewhere (Scarbrough & Kyratsis, 2022; Horton, Illingworth & Warburton, 2018).

Numerous studies have examined the difficulties of translating the success of clinical decision support tools from one site to another. In particular, the strong interdependence between

technical, social, and organisational dimensions suggests that there is no single prescriptive approach to promoting the spread of such tools (Greenhalgh et al., 2004; Berg 2001). Moreover, AI providers seeking to commercialise their products are confronted with varied implementation contexts that render the spread of technology across organisations highly complex (Pumplun et al., 2021; Shaw et al., 2019). Complexity science (Kauffman, 1995; Mainzer, 1997) offers a conceptual framework to understand these contexts as "an intrinsic part of a complex system; a dynamic environment that must be factored in for any intervention to be successfully taken up" (Braithwaite et al., 2018, p. 7).

In the present study, we draw on complexity science and qualitative research methods with the aim of understanding how providers of AI-enabled diagnostics perceive and navigate the spread of AI in complex healthcare systems. Much of the previous literature has focused on the perspective of adopting organisations (Lebcir et al., 2021; Watson et al., 2020; Weinert et al., 2022). In contrast, we explore the perspective of AI providers and their emerging practices as a form of self-organisation, echoing the conviction of Lanham et al. (2013, p.195) that "understanding self-organisation could lead to implementation designs that recognize the importance of local contexts, increasing the likelihood of achieving scaleup". Our results therefore contribute to a better understanding of this new group of stakeholders and how their practices may shape healthcare systems and the spread of AI-enabled diagnostics.

Our results highlight the challenges perceived by AI providers as they seek to promote the spread of AI-enabled diagnostics in the sociocultural, technological, and institutional subsystems of complex healthcare systems. We illustrate the perspectives of AI providers as they address these challenges through emergent practices of stealth science, agility, and digital ambidexterity. Our results suggest that rather than seeking to exercise direct control over technology spread, AI providers are developing practices that allow them to navigate healthcare systems in a flexible and adaptive way. By outlining the implications of these practices for the AI adoption pathway, we

contribute to current theories of AI spread in healthcare, adding an overdue narrative of provider-driven, purposeful technology spread.

Theoretical Background

The slow spread of clinical decision-support tools in healthcare

Characterising the adoption journey of clinical decision-support tools is a known challenge. Previous research has long established that even well-performing decision-support tools often fail to be replicated across organisational boundaries (Dombal et al., 1972). Numerous models have attempted to identify factors that foster or hinder successful adoption (Ammenwerth et al., 2006; Tornatzky et al., 1990; Yusof et al., 2008). Although these models highlight different factors, they share a focus on the fit between technology and the implementation environment, revealing a range of interdependencies among different dimensions of technology adoption. Taking this notion one step further, Berg (2001) illustrates that this fit is the result of a socio-technical process that requires mutual adjustments of the implementation environment, its inhabitants, and the decision-support system. Similarly, in developing their holistic framework for the organisational adoption of AI-enabled diagnostics, Pumplun et al. (2021) illustrate how the adoption of these tools spans multiple dimensions, entailing a process of "continuous embedding". Processes of sensemaking, knowledge production, and changing belief systems defy boxes-and-arrows models because they involve redistributions of power and emotions, often played out via recursive practices and nonlinear change of technology use over time and scale (Greenhalgh & Stones, 2010). Together, these factors make it difficult to replicate examples of successful technology implementation. This difficulty is compounded in the case of AI due to its unprecedented autonomy, ability to learn, and inscrutability, which are seen as pushing the boundaries of healthcare and medical ethics (Berente, Gu & Recker, 2021). In particular, medical technology incorporating AI poses unique challenges in terms of clinical responsibility, black-box decision-making, and data consent (Shaw et al., 2019). These uncertainties constitute also risks and sources of mistrust that may deter prospective users.

Controlling the spread of AI technologies across organisational boundaries is particularly difficult because it requires de-localising locally embedded and highly context-dependent tools. The established research divide between implementation science and theories of technology diffusion challenges our understanding of the interconnected processes between the organisational and system levels. Conjunctive thinking can thus help us explore the sociotechnical processes behind user–technology interactions distributed across multiple system levels (Essén & Värlander, 2019; Cruz, 2022; Lupton & Jutel, 2015). Recent approaches to marry both perspectives via an 'embedding' logic (Scarbrough & Kyratsis, 2022) allow us to examine mechanisms of system-wide spread that can scale local implementation knowledge and efforts.

A complexity science approach to understanding AI spread in healthcare

By regarding technology spread as complex patterns and processes situated in local interactions (Greenhalgh et al., 2004), complexity science (Kauffman, 1995; Mainzer, 1997) provides a conceptual framework for understanding the challenges of AI spread. Complexity is defined as "the dynamic and constantly emerging set of processes and objects interacting with each other and being defined by these interactions" (Cohn et al., 2013, p. 42). From this perspective, healthcare systems are complex because the actions of each agent redefine the context across multiple levels and subsystems (Plsek & Greenhalgh, 2001; Greenhalgh & Papoutsi, 2019). Beyond enabling conjunctive thinking, a complexity approach highlights the unpredictability that arises from agency and tensions in healthcare, both of which are underdeveloped in current models of AI spread.

Agency is defined as the cognitive, motivational, and emotionally driven intentional behaviours that actors employ to achieve their end goal (Byrne & Callaghan, 2013; Long, McDermott & Meadows, 2018). Drawing on notions of material agency, it is also assumed that technology itself accommodates or resists certain practices of human agents (Pickering, 1993). Providers of AI-enabled diagnostics are actors within complex healthcare systems who have an agenda to deploy their technology across the largest possible number of organisations. Whether their behaviours are

motivated by profit-maximising goals or by conviction in their technology's purpose, we assume that these behaviours are intentional and directed at increasing and perpetuating the spread of their technology. AI providers thus use their agency to deliberately intervene in the technology translation and adoption pathway (Sendak et al., 2020).

At the same time, commercialisation of AI in healthcare requires considerable flexibility and reinvention of AI providers, as changes in the implementation environment impact the performance of algorithms (Åström, Reim & Parida, 2022). AI providers can thus be seen as intermediaries whose experiences capture learnings across organisational implementation contexts (Scarbrough & Kyratsis, 2022). However, despite their inter-organisational experiences, technology providers remain a "surprisingly underused resource" in research on technology spread (Cresswell et al., 2015). This is particularly true with regard to providers of diagnostic AI considering the relatively recent emergence of commercial ventures in this field (Zahlan, Ranjan, & Hayes, 2023). By focusing our inquiry on the perspectives and actions of these technology providers, we may gain insights into providers' impact on AI spread in healthcare.

Taking a complexity science approach to this research question also entails exploring the tensions that arise from the introduction of new technologies (Greenhalgh & Papoutsi, 2018). Bahar (2018, p. 361) describes what she calls 'essential tensions' arising in complex systems: "a balance between cooperation and competition, a balance between interactions at the local level [...] and external pressures originating beyond these local interactions. [... The] balance of these apparently opposing drives plays a crucial role in the emergence of an ensemble of elements into a new individual in its own right". Emergent properties and behaviour describe the ability of small independent system parts to self-organise and thereby transcend the "sum of [their] parts" (Paina & Peters, 2012). From such emergent behaviour, new practices and patterns evolve at a system level which often elude top-down regulation or control (Braithwaite et al., 2018).

In essence, complexity science highlights the unpredictability of introducing a new technology into healthcare systems. This notion makes the agency of AI providers a focus of our inquiry into the spread of diagnostic AI.

Methods

Research design

Qualitative research of complex systems requires focusing on nonlinearity, identifying patterns across multiple levels, shifting foreground and background, and understanding that patterns change under different circumstances (Anderson et al., 2005). In practical terms, we achieve this by drawing on various sources of data that capture the practices of AI providers from multiple angles.

To fulfil our aim of examining the impact of AI providers' perceptions and practices on the spread of AI-enabled diagnostics, we defined stakeholders who were directly involved in developing and selling the technology as the appropriate informants for our interviews. As we were interested in the spread of AI and were seeking to capture AI providers' perceptions of real-life provider–user interactions, we included only companies that had already commercialised their technology. After a horizon scan of diagnostic AI providers based in Europe, we contacted all 19 companies that met this criterion and invited them to participate in our study. Of these companies, 14 accepted our invitation, covering different medical specialties and operating across various European countries.

Data collection

Data triangulation was crucial to our analysis because we used diverse data sources and multiple methods to ensure an adequately sophisticated representation of the complexity inherent to the phenomenon under study (Braithwaite et al., 2018; Greenhalgh & Papoutsi, 2019). Our primary source of data was one-on-one interviews with representatives of the participating companies. In total, we conducted 17 of these interviews with an average length of 50 minutes between April and December 2022. Interview partners were selected based on their strategic role in the company. We

developed a semi-structured interview guide comprising questions about the process of ensuring patient access, the specific value proposition of the product, the management of user interactions, and the strategic goals of promoting AI-driven tools in healthcare. All interviews were conducted online in English and were audio-recorded and transcribed with the consent of the interviewees.

We triangulated our data by complementing these interviews with multiple data sources. The first of these was interviews with two directors at a leading pharmaceutical company partnering with AI providers to diagnose rare disease patients, as well as with a hospital that had previously used AI-enabled diagnostics supplied by one of the interviewed companies. By including these adopters in our analysis, we aimed to reflect the dyadic relationship and its inherent interdependencies (Yin, 2003) and thus provide a multidimensional view of the practices of technology developers. We abstained, however, from exclusively collecting dyadic data because identifying the appropriate technology adopters would have required a snowball technique that depended on the recommendations of the participating technology providers. We considered that such an approach would potentially introduce bias to our study because technology providers might tend to refer us to successful cases of implementation.

As an alternative way to introduce the clinician's perspective to our research and thus critically reflect on our interview data, we organised an online focus group with six physicians who had practical experience using AI-enabled diagnostics. The physicians were from different European countries and practised different specialties, and all of them had indicated during an earlier online survey on the use of AI to diagnose rare diseases that they would be willing to take part in a follow-up focus group. For 90 minutes, participants discussed the spread of AI-enabled diagnostics in healthcare and their experiences cooperating with AI providers. The discussion was facilitated by the research team and guided by prompts to identify aspects such as the biggest hurdles to embedding AI technology in healthcare, the potential of AI to improve clinical practice, and the role of the physician in the implementation of AI tools. Mini focus groups have been shown to be

particularly well suited for prompting discussion about specialised experiences and creating an intimate atmosphere, thereby limiting negative group effects (Onwuegbuzie et al., 2009).

Lastly, we collected archival data, including 74 online blog posts by the participating AI developers, public guidance on the use of automated diagnosis tools, and white papers and peer-reviewed articles published by the technology developers that provided evidence on the performance or use cases of their algorithms. All data sources are listed in Table 1-1.

Table 1-1 Data sources (paper 1).

17 interview transcripts
10 CEOs of AI providers
1 Business & Product Lead of AI provider
1 Co-founder and Deputy Director of AI provider
1 Global Business Developer of AI provider
1 Innovation Program Leader of AI provider
2 Directors of large pharmaceutical company
1 Physician in adopting organisation
1 focus group transcript (5 attending physicians; 90 minutes)
2 whitepapers on AI use for diagnosis
3 public guidelines on AI use for diagnosis
74 blog posts by AI providers

Data analysis

We conducted a thematic analysis of our qualitative data following the recommendations of Gioia, Corley and Hamilton (2013). Through multiple iterative rounds of analysis and theory building, we critically examined our findings with the aim of faithfully depicting the complex and variable context of our research setting (Golden-Biddle & Locke, 2007). Adopting an inductive approach,

we began with a first round of "open coding" (Corbin & Strauss, 1990) that centred on actors' subjective reality (Gioia, Corley & Hamilton, 2013) and allowed us to derive rich first-order concepts. Subsequently, we aggregated and abstracted these concepts into second-order themes. This process was guided by an iterative method that involved continuous challenge and restructuring as we compared the fit of each new data fragment into the existing categories (O'Reilly, Paper & Marx, 2012). The emerging themes related to different processes and ideas for embedding AI technology in healthcare systems. We then used the ontology of complexity science to identify three aggregate dimensions, which captured the highest level of abstraction in our data structure. Our final data structure is illustrated in Figure 1-1.

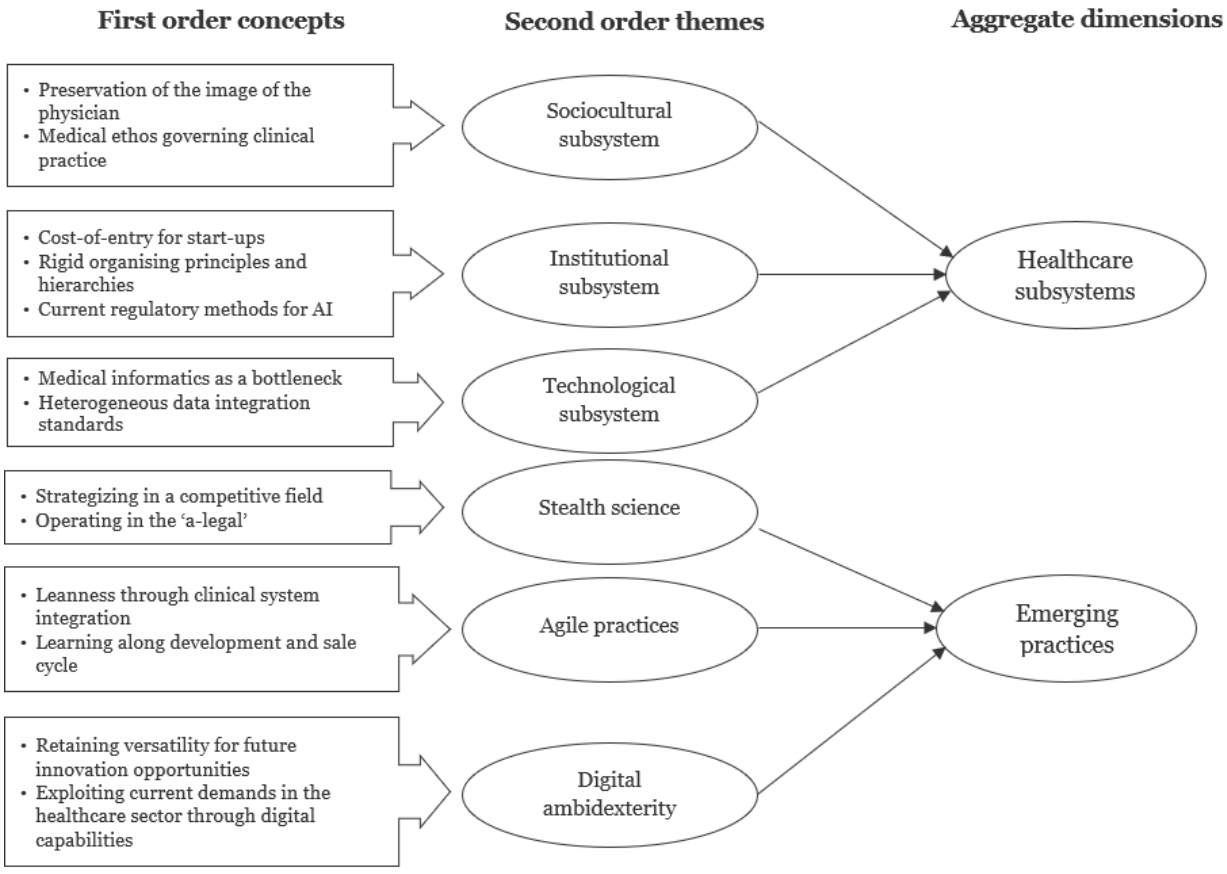


Figure 1-1 Data structure.

Lastly, we established links between the different levels and dimensions of our data structure. This process required a high level of familiarity with the precise definition and scope of each concept, theme, and dimension. Because theory mainly emerges from the links between categories (Gioia, Corley & Hamilton, 2013), we frequently revisited the source material to uncover how different categories related to each other. This practice enabled us to establish a theoretical abstraction of a provider-centric perspective on promoting AI spread in healthcare.

Results

In the first part of this section, we present how the participating AI providers made sense of complex healthcare systems as they operated within three distinct subsystems of healthcare: sociocultural, technological, and institutional. Subsequently, we illustrate how the challenges they perceived in these subsystems contextualised their agency. Lastly, we describe how their responses to these challenges culminated in emergent practices.

Subsystems of complex healthcare systems

Sociocultural subsystem

In their interviews, AI providers discussed various mental models and belief systems related to healthcare delivery. Their views encompassed ethical and moral codes, as well as perspectives on the roles of different agents in healthcare systems. We classified these perspectives as part of a *sociocultural subsystem* of healthcare. A dominant theme among AI providers was the current medical ethos, a set of jointly agreed and implicitly codified rules about how healthcare is to be practiced. In particular, certain role interpretations and related processes of sensemaking by physicians were seen by AI providers as restricting the spread of AI in healthcare. While AI providers recognised that healthcare professionals bear considerable responsibility in their daily decision-making, they also believed that the prevailing medical ethos influenced physicians' willingness to embrace risk and disruptive change in clinical practice. Because black-box decision-making is an inherent characteristic of advanced AI, the blurred boundaries between clinical responsibility and the opacity of diagnostic results were considered by the AI providers to be

incompatible with the medical ethos. One interviewee explained how discussions of diagnostic errors elicited negative feedback from physicians.

"In the early days, we would focus on diagnostic error. We'd say the problem is loads of diagnostic errors. And, of course, people interpret that, and they get very prickly: 'I'm comfortable that you're talking about diagnostic error because it's always somebody else.' It's not ever them that makes a diagnostic error – it's always somebody else. And if you talk to the GPs, they say, 'Yeah, it's not really for me. But I think the guys at the hospital would actually love it. Can you talk to the guys at the hospital?' So we did. [But then the people at the hospital said,] 'But the GPs, they would really love this.' So there's always somebody else that would use it […]. It's a bit like when seatbelts came out, you know? It was always, 'My brother is a terrible driver. He needs it, but I don't need it.' It's basically the same thing. So, in the early days, we did talk about diagnostic error, and that was a mistake." (CEO AI provider No. 14)

AI providers also appeared to attribute the small error margins that physicians allow themselves in their work to medical ethos. For example, one interviewee believed that the high stakes associated with accurate diagnoses act as a barrier to advancing digital innovation.

"I think doctors know what they want, but they are difficult to work with in innovation because they normally want perfection, and they don't accept error a lot. That's the kind of thing that really kills innovation when you talk about pilots and these kinds of things. So I think it's a difficult environment to innovate in. It's great, you can do it, but it takes a lot of time and effort. It's exhausting." (CEO AI provider No. 9)

Furthermore, AI providers perceived a potential fear among physicians that using AI-enabled technology in front of patients might harm their reputation. AI providers interpreted the resulting tension as physicians' attempt to retain their expert position and reproduce patient–physician hierarchies. AI's potential to empower patients and thus shift the balance of power in the patient–physician relationship was seen as a root cause of this tension.

"Culture is always a problem in medicine. So, for example, clinicians are scared of patients getting a symptom checker. [For them it's] just like opening a Pandora's box, because normally there's this relationship of the doctor and the patient. […] The phrase that I keep coming back to that encapsulated it so beautifully: the doctors need to get off their pedestals, and the patients need to get off their knees. It's this cultural difference." (CEO AI provider No. 14)

While this fear was not echoed by the physicians who participated in our focus group, the introduction of AI implies potential shifts in power dynamics beyond the patient–physician relationship. Indeed, focus group participants spoke of power redistributions between themselves and the technology, suggesting that the role of the sociocultural system in accommodating autonomous technology in healthcare requires further exploration.

Technological subsystem

We defined the second subsystem of complex healthcare navigated by AI providers as the *technological subsystem*, pertaining to technical infrastructure, standards, and processes in healthcare. Here, AI providers referred to two main barriers to AI-enabled diagnostics: a bottleneck in medical informatics and the heterogeneity of data integration standards. Medical informatics encompasses the medical informatics staff, resources, infrastructure, and capabilities of healthcare organisations. Medical IT departments rather than physicians were perceived by AI providers as gatekeepers due to their control over system integration processes and *de facto* data ownership. One technology provider described how medical informatics departments fulfil their gatekeeping role by regulating data and technology access.

"I would say that the first thing the IT department has to do is to anonymize the information and give us access to it, even when it's not ours. I will repeat it one hundred times: It's theirs, but we need to read it. Otherwise, we cannot apply our algorithm. So they have to do some informatics activities to be able to provide us access to it, and that takes a bit of time. And the IT departments are always overwhelmed, so we have to be sure that they see the benefits long term because it's a one-time effort, and then it's forever." (CEO AI provider no. 9)

The second barrier identified by AI providers was the diversity of rules and practices related to data formats across healthcare systems and jurisdictions, resulting in heterogeneous data integration standards. At the lowest levels of integration, healthcare data were not yet fully digitalised, thus preventing their use by AI-powered diagnostic support tools. At the other end of the spectrum, fully integrated IT systems were seen by AI providers as preventing the integration of externally developed algorithms.

Institutional subsystem

We found that by referring to the distribution of power and formal regulation of the system, AI providers were describing an *institutional subsystem* in healthcare. One frequently perceived barrier to technology spread in this subsystem was the perseverance of rigid organising principles. Providers of AI-enabled diagnostics advocated a preventative approach to medicine, which they interpreted as being incompatible with the prevailing curative paradigm in healthcare. Slow sales and R&D cycles were often attributed to this incompatibility.

Interviewees also highlighted the rigidity of regulations governing the use of AI in healthcare as a barrier. In a European context, AI-enabled software is regulated as a medical device, which implies strict requirements for developing and commercialising the technology. This was seen as being in stark contrast to the 'fail fast and break things' approach of AI-enabled innovation. Due to institutional and regulatory hierarchies in healthcare, AI providers described a considerable cost of entry, particularly for start-ups, which prevented them from interacting with regulators and thus from pursuing change. Because AI presents an extremely fast-moving technological domain, one respondent described their frustration in navigating this subsystem from the lower hierarchical levels and with such high costs of entry.

"I've been in think tanks where I'm frustrated by the fact that when I say what we do, people seem to think it's something that's going to happen in five or ten years' time. We're doing it now, so why not ask us what to do? Because if you still think it's happening in the future, you've missed the boat already. So this is the problem: Policy-makers will talk to the big people [...] with big

money. And they don't talk to people who can actually implement it. […] So the only people that really engage seem to be the big pharmaceutical companies because they've got plenty of capacity to spend on that. The cost of entry for conversations about regulation is so high because you have to have people literally dedicated to it." (CEO AI provider No. 10)

Emergent practices of AI providers in healthcare

Our findings suggest that by linking and scaling local implementation efforts, technology providers seek to *embed* AI in healthcare. During this embedding process, AI providers are confronted with negative system feedback whereby AI is perceived as incompatible with the context of different healthcare subsystems. The resulting tensions slow down or even prevent the boundary-spanning work of spreading AI across organisations. In turn, our findings indicate that these perceived tensions give rise to *emergent practices*, or patterns of self-organisation by AI providers, in the joint pursuit of overcoming negative system feedback.

Stealth science

First, we observed *stealth science*, defined as a lack of transparency around the development of scientific and technical capabilities and motivated by the desire to protect trade secrets or avoid regulatory scrutiny (Sendak et al., 2020). Among the AI providers participating in our study, the use of stealth science was justified by the need to strategize in an increasingly competitive field – indeed, as part of an arm's race to develop the most scalable, user-friendly, and reliable AI-enabled diagnostic support on the market. Moreover, technology providers pursued stealth science by operating in the 'a-legal'. One respondent explained how stealth science from their point of view is, in fact, an inherent part of technological innovation.

"The majority of the great achievements in innovation, they happen in the grey areas, in the 'a-legal', where [things are] not legal or illegal. If you really want to innovate, you have to assume that for some time you're going to work in a grey area – not doing anything unethical or illegal – but in a grey area until things are legislated. And that's great. If you're playing in a place that isn't legislated, you're probably innovating. If you're playing somewhere where [things] are

black and white, you're probably not innovating, because it means someone has thought about it already." (CEO AI provider No. 9)

In short, stealth science can emerge as a practice in contexts where the institutional subsystem is seen as threatening to impose rules on technology providers regarding the use and commercialisation of their technical capabilities. Importantly, the inhibitory effect of strict top-down regulation was exacerbated, in the view of AI providers, by the lack of opportunity to interact with regulators.

Agile practices

We additionally observed the emergence of *agile practices*, which can be defined as project management and software development approaches anchored in the principles of learning and leanness. Both of these principles featured prominently in technology providers' descriptions of their efforts to spread AI-enabled diagnostics. The principle of learning was evident throughout the sales and development cycle of AI tools: Because large training data sets are needed to power predictive AI models, simultaneously selling and developing the technology was standard practice among interviewed providers. This dual approach facilitated the continuous integration of feedback from clinicians and IT departments, fostering continual product improvement. The principle of leanness was manifested primarily through system integration. AI providers took deliberate steps to ensure that operational barriers to using their AI tools would be as low as possible. As one respondent pointed out, this emphasis on leanness was crucial for circumventing technological barriers.

"I think by now we've seen all systems that exist, and we're able to extract the data in the format that you prefer. Some organisations want to give us raw information. Sometimes organisations want to give us access to the database. Some organisations even gave us plain text, and we really adapted to this. We have different methodologies to transform all this data into one single common data model. So we're not really playing the game of data standards because we don't really need them." (CEO AI provider No. 8)

Agile practices appear to have emerged because AI providers had to navigate different technical implementation settings. We found that they frequently encountered heterogeneous data integration standards and bottlenecks in medical informatics. However, AI providers felt that these challenges presented opportunities for transferrable and scalable learning, even though this learning must be adjusted to different contexts.

Because organisational contexts in healthcare are typically diverse, collaboration between technology providers and healthcare organisations demands an agile approach to implementation. The emergence of agile practices enables providers to accommodate the fragmented digital and data landscape in different healthcare settings. At the same time, providers appear to adjust their communication strategies when interacting with collaborating physicians, allowing them to navigate the sociocultural system more easily.

Digital ambidexterity

The third emergent practice revealed by our data was *digital ambidexterity,* which describes the dual pursuit of efficiency and innovation through digital capabilities (Magnusson, Päivärinta & Koutsikouri, 2021). Achieving and maintaining this balance is generally considered extremely challenging due to resource constraints (O'Reilly & Tushman, 2008). We observed digital ambidexterity emerge among participating AI providers as they succeeded in pursuing two seemingly opposed strategies: the short-term aim of exploiting their technological capabilities to make themselves invaluable stakeholders for healthcare providers, and the long-term aim of exploring innovation opportunities. One respondent described how AI providers can exploit other agents' high opportunity costs of accumulating AI capabilities.

"And that's another reason why hospitals partner with [AI provider], right? Because I mean, you don't want trained physicians to develop machine learning and AI applications by themselves. There is a very high cost when you ask people to do something they haven't done before. I mean, look at us. We are one of the biggest pharmaceutical companies, and although we do have some machine learning and AI capabilities in-house, we prefer to work with [AI provider] because of

the time it would take us to reach the levels at which [software name] is today. It would be associated with a great opportunity cost. So at the end of the day, you need to find the right mix of partners and make sure that each one of them focuses on what they can do best." (Director pharmaceutical company No. 1)

A similar sentiment was shared by physicians in the focus group, as highlighted by one participant.

"I think [physicians] don't need to be experts in the process behind the algorithm, but we need to be sure that the algorithm itself is valid and gives results that we can rely on. We don't need any training per se *for developing these tools. [But] we [do] need, of course, collaboration with [AI] experts, who know what machine learning can give us." (Focus group participant No. 4)*

We also observed long-term strategies for exploring innovation opportunities. Participating AI providers emphasised their intent to exploit the versatility of their data analytic capabilities. Most of them had developed several distinct product versions of their algorithm yet maintained an open stance on which product direction to pursue in the future. One respondent noted how retaining this versatility broadened the market reach to a wider spectrum of potential technology users.

"The technology always works the same way. I would say that the way that it is integrated for each customer can be different because the goals of each customer are different. So, for example, an insurance company might just like to get faster triage and access for their members to in-network services. And a pharma company maybe just wants to find these undiagnosed patients around the world and point them towards information about the disease or patient associations." (CEO AI provider No. 5)

We found that digital ambidexterity emerged predominantly due to tensions in the sociocultural system. Participating AI providers perceived physicians as being resistant to AI technology due to a fear that it might harm their reputation or that using it might violate the prevailing medical ethos. Our data suggest that digital ambidexterity allows technology providers to surmount such barriers by exploiting short-term needs dominating the healthcare market, such as demands to resolve

inefficiencies in healthcare provision, knowledge fragmentation, and the lack of automatization of time-intensive routine processes. It would seem that ambidextrous practices simultaneously enable AI providers to explore new use cases with higher social acceptance rates in the long term. This is either achieved by exploring innovation opportunities in the clinical setting or by targeting other customer bases such as health insurance or pharmaceutical companies. Such collaborations typically receive less public attention and may therefore open revenue streams less subject to regulatory scrutiny.

Discussion

This study investigated how providers of AI-enabled diagnostics perceive and navigate AI spread in complex healthcare systems. Our theoretical model is rooted in complexity science and analyses the perspective of AI providers operating across local implementation contexts to embed their technology in depth and at scale. Figure 1-2 summarises and illustrates our findings. Overall, our results reveal that stealth science, agility, and digital ambidexterity emerge as practices among AI providers to mitigate tensions arising from the introduction of AI in the sociocultural, technological, and institutional subsystems of healthcare.

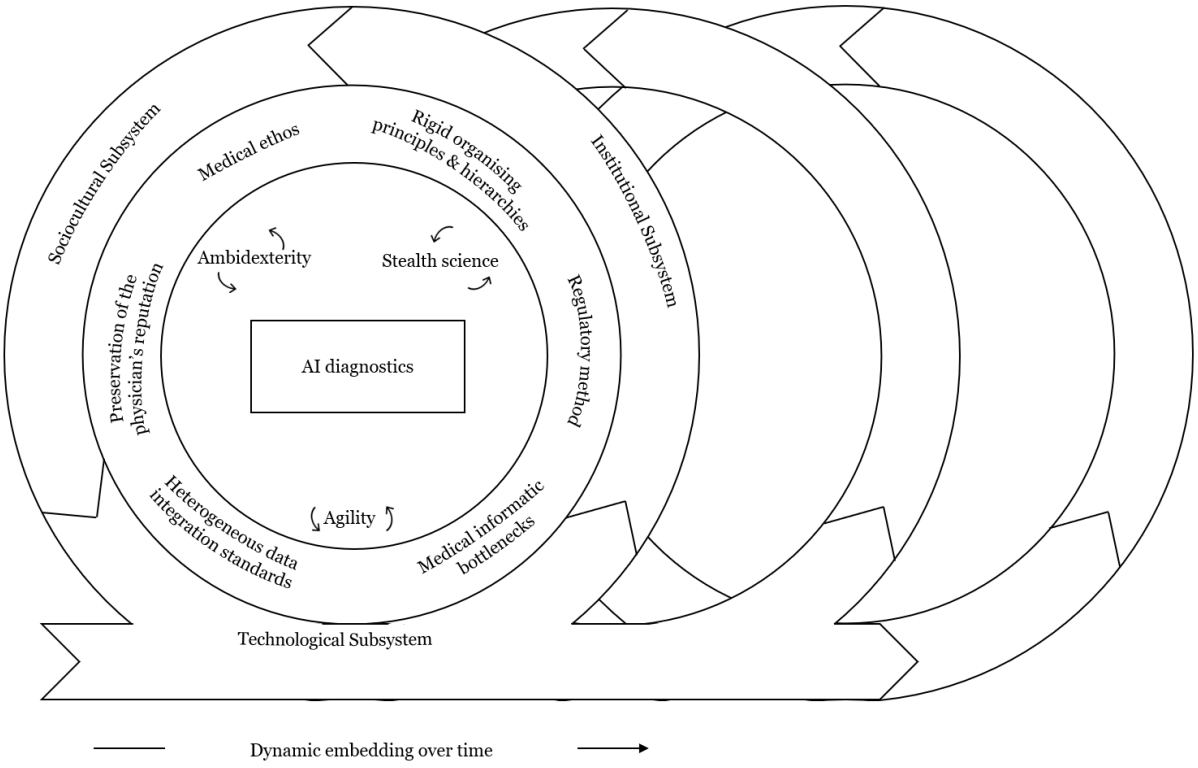


Figure 1-2 Theoretical model illustrating the dynamic embedding of AI-enabled diagnostics in healthcare.

We present healthcare as a complex system comprising different subsystems. In this way, we build on previous literature that has sought to disentangle implementation complexity by defining different dimensions of technology spread (Sittig & Singh, 2010; Tornatzky et al., 1990; Yusof Stergioulas & Zugic, 2007). We regard the three subsystems as an abstraction of the highly interdependent implementation context perceived by the technology providers. Our theoretical model also considers how interdependencies between the subsystems affect the context in which AI providers' agency is situated within each subsystem (Long, McDermott & Meadows, 2018). For instance, the perceived culture of risk avoidance characterising the sociocultural subsystem determines patterns within the institutional and regulatory subsystem; these patterns are then interpreted by AI providers as rigid and conservative regulations. In turn, the rules set by authorities influence the technological context of data integration practices across healthcare organisations. Importantly, our model anticipates a dynamic perspective, illustrated by system loops. AI spread is an ongoing process that assumes the continuous embedding of technology in a

changing healthcare system context. This implies the emergence of new practices over time that cannot be fully anticipated.

Overall, our results suggest that AI providers perceive complex healthcare systems as difficult to navigate. Adopting a complexity science approach, we initially contrasted the healthcare system's unpredictable uptake of a new technology with AI providers' ambition to promote and perpetuate technology spread. Our results suggest that AI providers' local practices, which are aimed at achieving what is needed 'on the ground', culminate in new patterns of self-organisation. Indeed, the emergence of stealth science is a remarkable illustration of how the opposing forces of cooperation and competition described by Bahar (2018) can lead to systemic patterns of self-organisation among locally operating AI developers: At the micro level, each AI developer seeks to protect its competitive advantage in a tightly regulated market by guarding its technical capabilities. At the macro level, however, the aggregation of competitive behaviour, fuelled by collective discontent with current regulatory methods for AI in healthcare, incentivises providers to evade or precede regulation, thus jointly engaging in stealth science. Our results also imply that rather than seeking to exercise control over the complex implementation environment or its inhabitants, AI providers tend to develop common practices that afford them more latitude in their work of embedding AI across organisations. Stealth science, agility, and digital ambidexterity each extend their adaptability to variable conditions across implementation settings.

AI providers' use of these practices has several implications for the healthcare system as a whole and for AI spread in particular. Similar to Essén and Lindblad (2013), we observed how a state of "bounded instability" (Plowman et al., 2007) permits a system to oscillate between positive and negative system feedback. Our results illustrate the negative feedback perceived by AI providers in each subsystem of healthcare. Without reaching stability, the system *in flux* is caught in a paradoxical state: the spread of AI is stuck between acceleration and inertia. Emergent practices among AI providers work to shift the balance towards accelerated technology spread. At the same time, their own practices inadvertently render healthcare even more complex: technological

advances are obscured through stealth science, and ambidexterity entails the constant re-definition of the technology itself.

Previous research has found that the implementation of clinical decision support tools requires the demystification of the system (Liberati et al., 2017); however, our results suggest that the practices employed by AI providers may work to the contrary. Moreover, recent ideas of applying a 'systems' regulation approach to AI entail assessing AI in a clinical environment while considering the human and organisational factors that influence its performance (Gerke et al., 2020). Such an approach could reduce the flexibility and ability to improvise that AI providers seek because it would require much stricter adherence to an implementation protocol. Lastly, emerging practices may lead to unintended consequences due to interactions between system parts (Greenhalgh & Papoutsi, 2019). While some emergent practices are momentarily successful at resolving immediate tensions in the system, they can cause negative effects as the system dynamically evolves. For example, the constant re-balancing of innovation and efficiency through digital ambidexterity currently allows AI providers to avoid resistance in the sociocultural system but may, in the long run, dilute the value creation and value capture propositions necessary to engage other agents in the spread of AI.

Our results underscore that different agents are currently in the process of negotiating their own and AI's respective roles in healthcare (Sun & Medaglia, 2019). On the one hand, this implies continuous boundary setting through technological and regulatory means. Restricting access to data and maintaining conservative regulation of AI are examples of efforts to define the limits of AI in healthcare. On the other hand, the process of negotiation entails adapting the characteristics of AI in terms of transparency and agency to establish clear accountability towards patients. Although AI technology is already capable of fully automated decision-making, in the case of AI-enabled diagnoses, the final decision tends to rest primarily with healthcare professionals (Lupton & Jutel, 2015). Our results highlight how AI providers seek to mediate this process by resolving emergent tensions and, in doing so, promote the spread of AI. However, as part of a complex

system, AI spread is equally influenced by other sources of agency, which might work for, against, or in parallel with the agency of AI providers.

We consider our model specific to the spread of AI and therefore not applicable to general technology spread. As Hund et al. (2021) point out, there is a "remarkable interconnectedness between social actors and digital technologies". Our model accordingly seeks to reflect how AI technology, which is characterised by unprecedented technological agency, defines the action context of technology providers, and leads to unique emergent behaviours. While insights from complexity science may benefit general models of technology spread, its application requires a rich and nuanced exploration of the research artifact (Greenhalgh & Papoutsi, 2018).

Our study has implications for future research on the topic of AI spread in healthcare. We have contributed to current theories of emergence in healthcare (Essén & Lindblad, 2013) by illustrating emergent practices among AI providers directed at perpetuating technology spread. Due to market failures and the need to protect patients against the self-interest of different stakeholders, top-down healthcare regulation is valuable and needed. Future research should acknowledge emergent phenomena in healthcare and explore how they can be reconciled with necessary regulatory methods. This is particularly true for AI, where legislative efforts are relatively young, and more knowledge is needed to guide regulation to overcome risks of confirmation bias and avoid stealth science. Furthermore, we encourage our peers to embrace the idea of healthcare as a complex and dynamic system. While there will always be merit in boxes-and-arrows models where appropriate, opportunities to employ complexity science should be recognised more often, particularly when the available body of research reveals seemingly inexplicable tensions and paradoxes.

While our study makes important contributions to the literature on AI and technology spread in healthcare, it has several limitations that must be considered when interpreting its results. First, more use of dyadic data could have revealed a richer picture of the interactions between AI providers and healthcare organisations (Morgan et al., 2013). Our study therefore only represents the perspective of technology providers. Researchers with access to adopting organisations may

wish to enrich our findings with accounts of interactive processes from both perspectives. Moreover, our study is situated in one moment in time. We highlighted this aspect of our research by pointing out the novelty and rapidly evolving nature of the studied phenomenon. However, while our model anticipates dynamic changes, we cannot currently predict which new practices will emerge or how these will interact with other sources of agency. A longitudinal study could add content to the system 'loops' of our model and thereby contribute insights into how healthcare systems and the spread of AI-enabled technologies dynamically evolve.

Conclusion

In this study, we provide the first account of AI spread in healthcare from the perspective of AI diagnostics providers. Drawing upon a complexity science view that technology spread is probably unpredictable and difficult to manage, we contrasted AI providers' agenda of promoting AI use with the challenges they perceive when navigating healthcare systems. Our results suggest that AI providers, rather than attempting to exert direct control over adopters or AI adoption pathways, rely instead on strategies of stealth science, agility, and digital ambidexterity. While these strategies provide AI providers with flexibility when seeking to embed their technology across different implementation settings, they may raise concerns about future regulation and wider acceptance of AI in healthcare.

Bibliography

Ammenwerth, E., Iller, C. & Mahler, C. 2006. IT-adoption and the interaction of task, technology and individuals: a fit framework and a case study. *BMC medical informatics and decision making, 6,* 3. DOI: 10.1186/1472-6947-6-3

Anderson, R. A., Crabtree, Benjamin, F., Steele, D. J. & McDaniel Jr, R. R. 2005. Case Study Research: The View from Complexity Science. *Qualitative Health Research, 15*(5): 669–685. DOI: 10.1177/1049732305275208

Åström, J., Reim, W. & Parida, V. 2022. Value creation and value capture for AI business model innovation: a three-phase process framework. *Review of Managerial Science, 16*(7): 2111–2133. DOI: 10.1007/s11846-022-00521-z

Bahar, S. 2018. *The Essential Tension*. Dordrecht: Springer Netherlands. DOI: 10.1007/978-94-024-1054-9

Berente, N., Gu, B. & Recker, J. 2021. Managing Artificial Intelligence. *MIS Quarterly*, 45(3he). DOI: 10.25300/MISQ/2021/16274

Braithwaite, J., Churruca, K., Long, J. C., Ellis, L. A. & Herkes, J. 2018. When complexity science meets implementation science: a theoretical and empirical analysis of systems change. *BMC Medicine, 16*(1). DOI: 10.1186/s12916-018-1057-z

Byrne, D. S. & Callaghan, G. 2013. *Complexity Theory*. Hoboken: Taylor and Francis. DOI: 10.4324/9780203519585

Chen, H., Chiang, R. & Storey, V.C. 2012. Business Intelligence and Analytics: From Big Data to Big Impact. *MIS Quarterly, 36*(4): 1165. DOI: 10.2307/41703503

Cohn, S., Clinch, M., Bunn, C. & Stronge, P. 2013. Entangled complexity: why complex interventions are just not complicated enough. *Journal of health services research & policy*, *18*(1): 40–43. DOI: 10.1258/jhsrp.2012.012036

Corbin, J. & Strauss, A. 1990. Grounded Theory Research: Procedures, Canons and Evaluative Criteria. *Qualitative Sociology, 19*(6): 418–427. DOI: 10.1515/zfsoz-1990-0602

Cresswell, K. M., Lee, L., Slee, A., Coleman, J., Bates, D. W. & Sheikh, A. 2015. Qualitative analysis of vendor discussions on the procurement of Computerised Physician Order Entry and Clinical Decision Support systems in hospitals. *BMJ open*, *5*(10): e008313. DOI: 10.1136/bmjopen-2015-008313

Cruz, T. M. 2022. The social life of biomedical data: Capturing, obscuring, and envisioning care in the digital safety-net. *Social science & medicine, 294*: 114670. DOI: 10.1016/j.socscimed.2021.114670

De Dombal, F. T, Leaper, D. J., Staniland, J. R., McCann, A. P. & Horrocks, J. C. 1972. Computer-aided Diagnosis of Acute Abdominal Pain. *Br Med J, 2*(5804), 9–13. DOI: 10.1136/bmj.2.5804.9

Essén, A. & Lindblad, S. 2013. Innovation as emergence in healthcare: unpacking change from within. *Social science & medicine*, *93*: 203–211. DOI: 10.1016/j.socscimed.2012.08.035

Essén, A. & Värlander, S. W. 2019. How technology-afforded practices at the micro-level can generate change at the field level: Theorizing the recursive mechanism actualized in Swedish rheumatology 2000–2014. *MIS Quarterly, 43*(4), 1155-1176. DOI: 10.25300/MISQ/2019/12164

Garbuio, M. & Lin, N. 2019. Artificial Intelligence as a Growth Engine for Healthcare Startups: Emerging Business Models. *California Management Review, 61*(2): 59–83.

Gerke, S., Babic, B., Evgeniou, T. & Cohen, I. G. 2020. The need for a system view to regulate artificial intelligence/machine learning-based software as medical device. *NPJ digital medicine, 3*: 53. DOI: 10.1038/s41746-020-0262-2

Gioia, D. A., Corley, K. G. & Hamilton, A. L. 2013. Seeking Qualitative Rigor in Inductive Research. *Organisational Research Methods, 16*(1): 15–31. DOI: 10.1177/1094428112452151

Golden-Biddle, K. & Locke, K. 2007. *Composing qualitative research* (2nd ed.). Thousand Oaks, Calif.: Sage. DOI: 10.4135/9781412983709

Greenhalgh, T. & Papoutsi, C. 2018. Studying complexity in health services research: desperately seeking an overdue paradigm shift. *BMC medicine, 16*(1): 95. DOI: 10.1186/s12916-018-1089-4

Greenhalgh, T. & Papoutsi, C. 2019. Spreading and scaling up innovation and improvement. *BMJ (Clinical research ed.), 365*: l2068. DOI: 10.1136/bmj.l2068

Greenhalgh, T., Robert, G., Macfarlane, F., Bate, P. & Kyriakidou, O. 2004. Diffusion of innovations in service organisations: systematic review and recommendations. *The Milbank quarterly*, *82*(4): 581–629. DOI: 10.1093/owc/9780199552351.003.0013

Greenhalgh, T. & Stones, R. 2010. Theorising big IT programmes in healthcare: strong structuration theory meets actor-network theory. *Social science & medicine*, *70*(9): 1285–1294. DOI: 10.1016/j.socscimed.2013.12.014

Horton, T. J., Illingworth, J. H. & Warburton, W. H. P. 2018. Overcoming Challenges In Codifying And Replicating Complex Healthcare Interventions. *Health affairs (Project Hope), 37*(2): 191–197.

Hund, A., Wagner, H.T., Beimborn, D. & Weitzel, T. 2021: Digital innovation: Review and novel perspective. *The Journal of Strategic Information Systems*, *30*(4): 101695. DOI: 10.1016/j.jsis.2021.101695

Kauffman, S. A. 1995. *At home in the universe: The search for laws of self-organisation and complexity* / Stuart Kauffman. New York, Oxford: Oxford University Press.

Lanham, H. J., Leykum, L. K., Taylor, B. S., McCannon, C. J., Lindberg, C. & Lester, R. T. 2013. How complexity science can inform scale-up and spread in healthcare: understanding the role of self-organisation in variation across local contexts. *Social science & medicine*, *93*: 194–202. DOI: 10.1016/j.socscimed.2012.05.040

Lebcir, R., Hill, T., Atun, R. & Cubric, M. 2021. Stakeholders' views on the organisational factors affecting application of artificial intelligence in healthcare: a scoping review protocol. *BMJ open, 11*(3): e044074. DOI: 10.1136/bmjopen-2020-044074

Lee, J., Suh, T., Roy, D. & Baucus, M. 2019. Emerging Technology and Business Model Innovation: The Case of Artificial Intelligence. *Journal of Open Innovation: Technology, Market, and Complexity*, *5*(3): 44. DOI: 10.3390/joitmc5030044

Liberati, E. G., Ruggiero, F., Galuppo, L., Gorli, M., González-Lorenzo, M., Maraldi, M., Ruggieri, P., Polo Friz, H., Scaratti, G., Kwag, K. H., Vespignani, R. & Moja, L. 2017. What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. *Implementation science*, *12*(1): 113. DOI: 10.1186/s13012-017-0644-2

Long, K. M., McDermott, F. & Meadows, G. N. 2018. Being pragmatic about healthcare complexity: our experiences applying complexity theory and pragmatism to health services research. *BMC medicine*, *16*(1): 94. DOI: 10.1186/s12916-018-1087-6

Lupton, D. & Jutel, A. 2015. 'It's like having a physician in your pocket!' A critical analysis of self-diagnosis smartphone apps. *Social science & medicine*, *133*: 128–135. DOI: 10.1016/j.socscimed.2015.04.004

Magnusson, J., Päivärinta, T. & Koutsikouri, D. 2021. Digital ambidexterity in the public sector: empirical evidence of a bias in balancing practices. *Transforming Government: People, Process and Policy*, *15*(1): 59–79. DOI: 10.1108/TG-02-2020-0028

Mainzer, K. 1997. *Thinking in Complexity: The Complex Dynamics of Matter, Mind, and Mankind* (3rd edn.). Heidelberg: Springer Berlin. DOI: 10.1063/1.4823421

Morgan, D. L., Ataie, J., Carder, P. & Hoffman, K. 2013. Introducing dyadic interviews as a method for collecting qualitative data. *Qualitative Health Research*, *23*(9): 1276–1284. DOI: 10.1177/1049732313501889

Onwuegbuzie, A. J., Dickinson, W. B., Leech, N. L. & Zoran, A. G. 2009. A Qualitative Framework for Collecting and Analyzing Data in Focus Group Research. *International Journal of Qualitative Methods*, *8*(3): 1–21. DOI: 10.1177/160940690900800301

O'Reilly, K., Paper, D. & Marx, S. 2012. Demystifying Grounded Theory for Business Research. *Organisational Research Methods*, *15*(2): 247–262. DOI: 10.1177/1094428111434559

O'Reilly, C. A. & Tushman, M. L. 2008. Ambidexterity as a dynamic capability: Resolving the innovator's dilemma. *Research in Organisational Behavior*, *28*: 185–206. DOI: 10.1016/j.riob.2008.06.002

Paina, L. & Peters, D. H. 2012. Understanding pathways for scaling up health services through the lens of complex adaptive systems. *Health policy and planning*, *27*(5): 365–373. DOI: 10.1093/heapol/czr054

Pickering, A. 1993. The Mangle of Practice: Agency and Emergence in the Sociology of Science. *American Journal of Sociology*, *99*(3): 559–589. DOI: 10.1086/230316

Plowman, D. A., Baker, L. T., Beck, T. E., Kulkarni, M., Solansky, S. T. & Travis, D. V. 2007. Radical Change Accidentally: The Emergence and Amplification of Small Change. *Academy of Management Journal*, *50*(3): 515–543. DOI: 10.5465/amj.2007.25525647

Plsek, P. E. & Greenhalgh, T. 2001. Complexity science: The challenge of complexity in healthcare. *BMJ (Clinical research ed.)*, *323*(7313): 625–628. DOI: 10.1136/bmj.323.7313.625

Pumplun, L., Fecho, M., Wahl, N., Peters, F. & Buxmann, P. 2021. Adoption of Machine Learning Systems for Medical Diagnostics in Clinics: Qualitative Interview Study. *Journal of medical Internet research*, *23*(10): e29301. DOI: 10.2196/29301

Raji, I. D., Kumar, I. E., Horowitz, A. & Selbst, A. 2022. The Fallacy of AI Functionality. *2022 ACM Conference on Fairness, Accountability, and Transparency*. New York, NY, USA: ACM. DOI: 10.1145/3531146.3533158

Scarbrough, H. & Kyratsis, Y. 2022. From spreading to embedding innovation in healthcare: Implications for theory and practice. *Healthcare management review*, *47*(3): 236–244. DOI: 10.1097/HMR.0000000000000323

Sendak, M. P., D'Arcy, J., Kashyap, S., Gao, M., Nichols, M., Corey, K., Ratliff, W. & Balu, S. 2020. A Path for Translation of Machine Learning Products into Healthcare Delivery. *EMJ Innovations*, *4*(1). DOI: 10.33590/emjinnov/19-00172

Shaw, J., Rudzicz, F., Jamieson, T. & Goldfarb, A. 2019. Artificial Intelligence and the Implementation Challenge. *Journal of medical Internet research*, *21*(7): e13659. DOI: 10.2196/13659

Sittig, D. F. & Singh, H. 2010. A new sociotechnical model for studying health information technology in complex adaptive healthcare systems. *Quality & safety in healthcare, 19*(Suppl 3), i68-74. DOI: 10.1136/qshc.2010.042085

Sun, T. Q. & Medaglia, R. 2019. Mapping the challenges of Artificial Intelligence in the public sector: Evidence from public healthcare. *Government Information Quarterly*, 36(2): 368–383. DOI: 10.1016/j.giq.2018.09.008

Sutton, R. T., Pincock, D., Baumgart, D. C., Sadowski, D. C., Fedorak, R. N. & Kroeker, K. I. 2020. An overview of clinical decision support systems: benefits, risks, and strategies for success. *NPJ digital medicine*, *3*, 17. DOI: 10.1038/s41746-020-0221-y

Tornatzky, L. G., Fleischer, M. & Chakrabarti, A. K. (Hrsg.). 1990. *Processes of technological innovation*. Lexington Books.

Watson, J., Hutyra, C. A., Clancy, S. M., Chandiramani, A., Bedoya, A., Ilangovan, K., Nderitu, N. & Poon, E. G. 2020. Overcoming barriers to the adoption and implementation of predictive modelling and machine learning in clinical care: what can we learn from US academic medical centers? *JAMIA open*, *3*(2): 167–172. DOI: 10.1093/jamiaopen/ooz046

Weinert, L., Müller, J., Svensson, L. & Heinze, O. 2022. Perspective of Information Technology Decision Makers on Factors Influencing Adoption and Implementation of Artificial Intelligence Technologies in 40 German Hospitals: Descriptive Analysis. *JMIR medical informatics*, 10(6). DOI: 10.2196/34678

Yin, R. K. 2003. *Case Study Research*: *Design and Methods* (5th edition). Thousand Oaks, LA: Sage. DOI: 10.3138/CJPE.BR-240

Yusof, M. M., Kuljis, J., Papazafeiropoulou, A. & Stergioulas, L. K. 2008. An evaluation framework for Health Information Systems: human, organisation and technology-fit factors (HOT-fit). *International journal of medical informatics*, 77(6), 386–398. DOI: 10.1016/j.ijmedinf.2007.08.011

Yusof, M. M., Stergioulas, L. & Zugic, J. 2007. Health Information System Adoption: Findings from a Systematic Review. *Studies in Health Technology and Informatics*, 129, 262–266. PMID: 17911719

Zahlan, A., Ranjan, R. P. & Hayes, D. 2023. Artificial intelligence innovation in healthcare: Literature review, exploratory analysis, and future research. *Technology in Society*, 74, 102321. DOI: 10.1016/j.techsoc.2023.102321

Paper 2

How social networks influence the local implementation of initiatives developed in quality improvement collaboratives in healthcare: A qualitative process study

---

Citation: Gillner, S., Wild E.M. 2024. How social networks influence the local implementation of initiatives developed in quality improvement collaboratives in health care: A qualitative process study. *Healthcare Management Review* *49*(2): 148-157. DOI: 10.1097/HMR.0000000000000400

Acknowledgements and funding: This work was supported by OptiMedis AG in the form of a forwarding agreement on the part of the funding agency Verband der Ersatzkassen e.V. (Association of Substitute Health Insurance Funds). The authors would like to thank Alexander Helmut Fauser for his assistance during the data collection and analysis. A preliminary working version of this paper was presented at the Annual Meeting 2023 of the German Association for Health Economics e.V. (dggö) in Hannover, Germany.

Abstract

Background: Quality improvement collaboratives (QICs) have facilitated cross-organisational knowledge exchange in healthcare. However, the local implementation of many quality improvement (QI) initiatives continues to fail, signalling a need to better understand the contributing factors. Organisational context, particularly the role of social networks, in facilitating or hindering implementation within organisations, remains a potentially critical yet underexplored area to addressing this gap.

Purpose: We took a dynamic process perspective to understand how QI project managers' social networks influence the local implementation of QI initiatives developed through QICs.

Methodology: We explored the case of a QIC by triangulating data from an online survey, semi-structured interviews, and archival documents from 10 organisations. We divided implementation into four stages and employed qualitative text analysis to examine the relationship between three characteristics of network structure (degree centrality, network density, and betweenness centrality) and the progress of each QI initiative.

Results: The progress of QI initiatives varied considerably among organisations. The transition between stages was influenced by all three network characteristics to varying degrees depending on the stage. Project managers whose QI initiatives progressed to advanced stages of implementation had formed *ad hoc* clusters of colleagues passionate about the initiatives.

Conclusion: Implementing QI initiatives appears to be facilitated by the formation of clusters of supportive individuals within organisations; this formation requires high betweenness centrality and high network density.

Practice implications: Flexibly modifying specific network characteristics depending on the stage of implementation may help project managers advance their QI initiatives, achieving more uniform results from QICs.

Introduction

Many quality improvement (QI) initiatives in healthcare are developed through collaborative learning across organisational boundaries, and numerous models for this kind of knowledge exchange have been developed and tested in recent years (Nembhard, 2012). One of the most common models is the quality improvement collaborative (QIC) (Øvretveit et al., 2002). In QICs, QI project managers from each participating organisation establish connections with each other through regular meetings and progress check-ups, enabling the exchange of best practices, the sharing of knowledge, and even the development of individual or joint QI initiatives (Institute for Healthcare Improvement, 2003). However, there is evidence that many QI initiatives in healthcare, including those developed through QICs, fail to reach full implementation (Auerbach, Landefeld & Shojania, 2007; Nembhard, 2012; Hill et al., 2020; Aunger et al, 2021; Strating & Nieboer, 2013).

While the underlying causes of these implementation failures are complex and not well understood (Zamboni et al., 2020), organisational context has been identified as a crucial factor in fostering the conditions necessary for implementing QI initiatives (Coles et al., 2020). Coles et al. (2020) define this context as comprising individuals, interpersonal relations, institutions, and infrastructure in an organisation. Central to these interpersonal relations are social networks, which are known to facilitate the spread of new ideas and practices (Burt 1987). However, the ways in which social networks within an organisation influence the dissemination and implementation of QI initiatives, especially those developed in collaborative settings like QICs, remain underexplored.

To address this gap in the research, our study aimed to understand how the social networks of QI project managers affect the local implementation of QI initiatives developed through QICs. For this purpose, we examined the empirical case of a QIC in Germany and investigated the structural characteristics of social networks in each participating organisation and how these changed over time. Because the QIC in question involved only one project manager from each organisation, we focused in our analysis on the social network centred around each project manager. This allowed

us to explore how patterns of interaction among individuals in each network might create advantages and disadvantages for the project manager (Granovetter, 1973; Burt, 2000). We considered implementation in this context to be a dynamic construct, consisting of a sequence of stages, rather than a process leading only to a static outcome such as "success" or "failure". We therefore used a linear process theorizing style to understand how the structural characteristics of social networks influence the transition of a QI initiative from one stage of implementation to the next (Cloutier & Langley, 2020). The resulting model also allowed us to investigate whether and how project managers in each organisation modified their social networks over time. Our results suggest that project managers took actions within their own organisations to modify their networks so that these would have higher betweenness centrality and higher network density to progress through the consecutive stages of implementation.

Theory

Quality improvement collaboratives

In QICs, a QI project manager (henceforth: "project manager") and often other staff from each participating organisation engage in collaborative learning to acquire evidence-based knowledge with the aim of improving care processes in their own facilities (Institute for Healthcare Improvement, 2003). Beyond the transfer of knowledge, QICs seek to facilitate the social processes of organisational learning, the routinization of new organisational practices and, ultimately, behavioural changes among healthcare staff (Dückers et al., 2011). Often this takes the form of QI initiatives that are developed collaboratively within the QIC and are subsequently implemented in each organisation. Consequently, project managers seeking to implement such a QI initiative have to feed external inputs from the QIC back into their organisation. We assume that this transfer of inputs, such as ideas, from a QIC setting to an organisation depends substantially on the structural characteristics of each project manager's social network. Consequently, we anticipate that the progress of implementing a QI initiative will vary among organisations participating in the same QIC depending on the structure of each project manager's social network.

Social networks and their structural characteristics

Social networks are defined as collections of actors, referred to as "nodes", connected by ties that represent social relationships between individuals. An "egocentric network" refers to the network of a focal node (*ego*), and its "network structure" denotes the arrangement of ties connecting the individual to other nodes (*alters*) (McCarty, 2002). While network structure has been acknowledged to play a role in various domains, such as the translation of knowledge (Mascia, Pallotti & Dandi, 2018), organisational change (Tenkasi & Chesmore, 2003), and patterns of communication in learning collaboratives (Bunger & Lengnick-Hall, 2018), little is known about its impact on the implementation of QI initiatives developed through QICs.

When analysing the implementation of such QI initiatives, a critical aspect is the role of project managers because they are often (a) the primary representatives of an organisation and take part in QIC meetings and regularly communicate with other participants in the QIC and (b) the main agents of change within their respective organisations, and thus the individuals who lead the local implementation of their respective QI initiatives (Institute for Healthcare Improvement 2003). As a result, we chose to focus on the social network centred around each of these individuals in their respective organisations. This approach was facilitated by the fact that the QIC in our case study diverged from the traditional QIC approach by involving one project manager from each participating organisation instead of engaging teams with multiple participants per organisation. This allowed us to examine the social network structure of each project manager in our analysis rather than navigating through the complexities of multiple overlapping networks in a team-based setting.

By analysing social networks with the project manager as the "ego", we could examine how his or her *position and connections within each network* influenced the implementation process. While we acknowledge the potential influence of other network characteristics, we focus in this study on the three main characteristics of the structure of egocentric networks as defined by McCarty (2002): degree centrality, network density, and betweenness centrality.

Degree centrality describes the number of direct connections between the project manager and the alters, and thus the project manager's level of connectivity within an organisation. The degree centrality of a project manager provides an indication of his or her network activity and is thus linked to his or her influence (McCarty, 2002). In turn, *network density* refers to the number of ties that exist in a network out of the total number of potential ties among alters (McCarty, 2002). Dense networks have been shown to promote internal cohesiveness and therefore lead to similarity of beliefs and behaviour, facilitating group thinking and the building of norms and trust (Burt, 1987). Lastly, *betweenness centrality* in a social network measures how often a project manager appears on the shortest path between other pairs of nodes in the network (McCarty, 2002); nodes that fill the gaps (known as "structural holes") in a social network where there are few or no direct ties between non-adjacent nodes often exhibit high betweenness centrality (Burt, 2000). In other words, a high betweenness centrality indicates that the project manager is a key connector among his or her contacts, brokering knowledge and enabling the generation of new ideas by connecting individuals to nodes outside their interconnected group of peers (Granovetter, 1973).

Implementation and the influence of social networks

Implementation is a multidimensional concept that cannot be captured in a single event but rather progresses through different stages associated with specific goals and activities (Langley et al., 2013). Following the current literature, we divide the process of implementation into four consecutive stages: exploration, installation, initial implementation, and full operation (Fixsen et al., 2005). For a QI initiative to move from one stage of implementation to the next, a project manager must fulfil certain project needs, such as mobilizing resources or generating acceptance within an organisation (Cloutier & Langley, 2020; Perry-Smith & Mannucci, 2017). Table 2-i in the appendix illustrates the conditions that need to be met in each stage of implementation. Of course, implementation may stall, regress, or even fail if the necessary conditions for transitioning to the next stage are not met.

Due to the task contingency of social ties, network structures are thought to influence implementation differently during each stage depending on the required activities (Adler & Kwon,

2002). As project managers seek to navigate through different stages of implementation, their progress may be either facilitated or hindered by degree centrality, network density, or betweenness centrality. High degree centrality is often associated with visibility, prestige, and power, all of which serve important functions during the implementation of QI initiatives, such as access to resources (Glegg, Jenkins & Kothari, 2019). Dense networks are thought to achieve shared sense-making, the pursuit of common goals, and collective learning (Boland & Tenkasi, 1995). However, a project manager situated in a dense network may struggle to challenge the status quo or access information beyond his or her immediate circle in the organisation (Shea et al., 2018). Lastly, a project manager who bridges one or more structural holes and whose network therefore exhibits high betweenness centrality can exploit his or her position for knowledge brokerage and resource access across different units within an organisation (Burt, 2000).

At the same time, we acknowledge that a project manager participating in a QIC may seek to modify his or her social network to implement a QI initiative (Chambers et al., 2013). Indeed, Meltzer et al. (2010) suggest that participants in a QIC are expected not only to leverage their existing networks but also expand them in their organisation. In our analysis, we hypothesize that a project manager taking part in a QIC modifies his or her social network to facilitate the transition of a QI initiative from one stage of implementation to the next. To address our research question, we therefore chose a dynamic model (Langley, 2007) that considers activities aimed at modifying the social networks of project managers as they seek to implement QI initiatives developed through a QIC.

Methods

Research design and case selection

Our study aims to understand how the social networks of project managers affect the local implementation of QI initiatives developed through QICs. To facilitate an in-depth examination of the phenomenon of interest, we conducted a qualitative process study of a single case comprising one QIC involving multiple collaborating organisations, each represented by one project manager (Yin, 2014; Creswell & Poth, 2016). Specifically, we examined the implementation of 10 separate

QI initiatives that had been developed within the QIC, with each situated in one of the collaborating organisations. All organisations were hospitals or long-term care facilities located in Germany. The professional role of each project manager and the characteristics of each organisation are provided in Table 2-ii in the appendix.

The goal of each QI initiative was to implement a workplace health and well-being program for all staff of the respective organisation. Such programs consist of preventative and interventional strategies to improve the health and well-being of employees, and their successful implementation in healthcare facilities has been linked to enhanced organisational performance (Macik-Frey, Quick & Nelson, 2007).

Project managers in the QIC were afforded considerable autonomy in designing their interventions, leading to a variety of designs, from instituting scheduled recovery breaks for nursing staff to providing mental health support services. Importantly, the QIC curriculum did not prescribe any strategies for modifying the project managers' respective social networks in any way. We thus considered any network modifications initiated by a project manager to be self-guided and needs-driven rather than prescribed by the QIC curriculum. After participating in two months of online classes focusing on the content, management, and design of their individual QI initiatives, the project managers began to plan how to implement the initiatives in their respective organisations. Over the next four months, the project managers provided weekly reports to the collective and engaged in discussions about their initiatives with their counterparts. This planning and feedback phase was followed by an implementation phase, during which project managers sought to implement their respective QI initiatives in their own organisations.

Recruitment of participants

Before we started collecting data, the study protocol received ethics approval from the responsible board of the investigating organisation. To recruit participants, we used internal documents made available to us under a confidentiality agreement by the QIC organizers to identify all 16 project managers involved in the QIC. In October 2021, we sent out 16 invitations via e-mail, along with a study letter detailing the purpose and methodology of our study and followed up twice with non-

respondents via e-mail. Of the 16 contacted project managers, 10 accepted our invitation and took part in both the online survey and interviews, representing 10 organisations. We confirmed that the organisational types and sizes in our sample were representative of all organisations participating in the QIC, thereby minimizing selection bias.

Data collection

To ensure a comprehensive and rich case narrative, data triangulation was a fundamental aspect of our study design and methods. We accordingly drew upon multiple data sources for our analysis. The first of these was an online survey, which we conducted at two different time points to capture the characteristics of each project manager's social network at two (t_1; November 2021) and twelve (t_2; September 2022) months after the input phase of the QIC had ended. For this purpose, we adapted the visual network scales (VNS) developed by Mehra et al. (2014) to elicit information about project managers' social networks and any modifications made to those networks following participation in the QIC. VNS employ simple visual illustrations of structural network characteristics, and participants choose a representation of their own network using a Likert scale. As illustrated by Brands, Menges and Kilduff (2015), VNS can be adapted to illustrate different network qualities such as centralization and cohesion. Prior studies suggest that cognitive network representations are advantageous because they prioritize consciously available resources over analytical accuracy (McCarty, 2002).

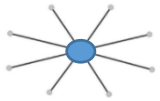
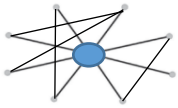
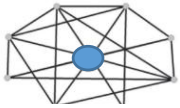
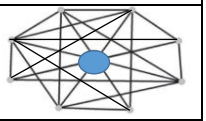
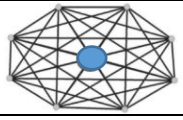
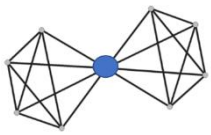
Density	
This question concerns the *interconnectedness* between all staff members in your organisation. Please indicate which of the figures best describes the interactions between all staff members in your organisation.	
1: In my organisation, staff members **do not** interact at all with each other.	
2: In my organisation, **few** staff members interact with each other.	
2: In my organisation, **many** staff members interact with each other	
4: In my organisation, **most** staff members interact with each other	
5: In my organisation, **all** staff members interact with each other	
Betweenness centrality	
The following figure shows two groups of people. The middle circle (in blue), which connects both groups of people, can be understood as a bridge between two groups. A *bridging function* can be fulfilled between your own team and another team, another department, or another location. You fulfil a bridging function if you are the only one in your team who regularly interacts with at least one employee from the other group. Please indicate how many bridging functions you fulfil.	
1: I fulfil **no** bridging function.	
2: I fulfil **one** bridging function.	
3: I fulfil **two to three** bridging functions.	
1: I fulfil **four to five** bridging functions.	
1: I fulfil **more than five** bridging functions.	

Figure 2-1 Visual network scales.

To operationalize network structure in our survey, we defined social ties as regular interactions occurring at least weekly between two individuals in an organisation (Burt, 2000). This criterion established a minimum frequency of interaction without delving into aspects such as the depth and nature of the relationships. In accordance with Meltzer et al. (2010), we operationalized the structural measures of degree centrality, network density, and betweenness centrality using VNS

to reflect network characteristics that potentially facilitated or hindered the progress of a QI initiative from one stage of implementation to the next (Figure 2-1).

Our second source of data was from two rounds of semi-structured online interviews, which we conducted with the project managers alongside the survey to capture their implementation experiences at the same two time points (t1 and t_2). Each project manager provided written informed consent for us to audio record, transcribe, and anonymize their interview for scientific purposes. Interviews lasted 30 minutes on average.

We developed a semi-structured interview guide to explore the progress of implementation, challenges encountered by the project managers during the different implementation stages, the strategies they employed to implement their QI initiative, and the role of social interactions within the project managers' respective organisations in driving implementation forward. Both the survey and interview material underwent pre-testing for validity and suitability in terms of the project managers' comprehension. During the second round of the interviews, we discussed our initial findings with the project managers to identify whether their own perceptions aligned with our abstractions of the implementation process in their organisations, aiming to strengthen the credibility and validity of our results.

Our third source of data comprised a set of 43 archival documents, including records of knowledge exchange among the participating project managers, documentation of implementation progress, and monthly phone check-ins by QIC organizers with each project manager during the implementation stage. Data from the documents covered the entire two-year process, starting from the early planning stages of the QIC, including the recruitment of project managers and extending to the closing workshop, which marked the official conclusion of the active QIC phase. This enabled us to provide a longitudinal account of the implementation of each QI initiative in each organisation. Moreover, we attended and documented the closing workshop, which involved presentations and discussions among all project managers regarding their respective interventions. We subsequently used the observational data to strengthen our analysis, thereby

adding a fourth data source to our collected materials. A comprehensive list of all data sources can be found in Table 2-1.

Table 2-1 Data sources (paper 2).

Data Source	Data Type
Interviews (N_{t1}=12, N_{t2}=5)	T1: 10 semi-structured interviews with QI project managers 2 semi-structured interviews with QIC coordinators T2: 5 semi-structured interviews with QI project managers
Online survey (N_{t1}=10, N_{t2}=5)	T1: 10 online surveys with QI project managers T2: 5 online surveys with QI project managers
Archival documents (N=43)	5 lesson plans (module 1-5) 3 transcripts of progress check-ups via phone 1 course book 20 forum posts 10 worksheets 3 transcripts of coordinated reflection meetings 1 internal evaluation report by the QIC coordinators
Observation minutes (N=1)	1 closing event with presentations by QI project managers

Data analysis

To explore how project managers' social networks influenced the local implementation of initiatives from the QIC, we adopted a synthetic research approach following the guidance of Langley et al. (2013). As described in the theory section, we view the implementation of a QI initiative as its progress from one stage of implementation to another in line with Langley's recommendations (2007; 2013). This progress was our outcome of interest. Accordingly, based on our longitudinal collection of data over several observation time points, we developed a linear process model by adapting Fixsen et al.'s staged implementation model. Our model identified the conditional network structures for a QI initiative to transition to the next stage of implementation, as well as any evidence of project managers deliberately modifying their social network to facilitate this transition.

All data were analysed using qualitative text analysis following a two-stage procedure. In the first stage, we conducted deductive structural coding (Saldaña, 2013) with two independent coders, who assigned content-based phrases to data segments. These deductive categories were deliberately broad and identified a QI initiative's stage of implementation, instances when social networks seemed to influence progress to the next implementation stage, and instances when progress to

the next stage appeared to depend on a project manager deliberately modifying his or her social network. In the second coding stage, we inductively developed subcategories to elaborate each code category, employing a process coding style (Saldaña, 2013). This approach revealed more nuanced subcategories; for instance, subcodes for network density described themes of community values, trust, and reliance on each group member. Intercoder reliability was assessed using Cohen's Kappa, resulting in a Kappa value of 0.85, indicating high intercoder agreement (Sun, 2011).

To analyse the coded material, we subsequently created visual 'storyboards' for each project manager. These storyboards mapped any changes in the participant's social network across the different stages of his or her QI initiative's implementation, creating a cohesive narrative. The storyboards also visually tracked instances on this timeline where project managers perceived that they had deliberatively modified their network to move their QI initiative to the next stage of implementation. We subsequently used the storyboards to identify common patterns and variations among participating organisations. During this process, we were conscious that participants may deviate from Fixsen et al.'s staged implementation model; however, we did not find any evidence of this in our data apart from several instances of discontinuities. When necessary, we referred to the source material to challenge our abstractions and interpretations of the data.

Results

In this qualitative process study of a QIC in the German healthcare sector, we examined structural characteristics of the social networks of QI project managers and how these characteristics contributed to the implementation of various QI initiatives developed through the QIC. We found substantial differences in the degree to which the implementation of each QI initiative progressed within each organisation despite the project managers' participation in the same QIC. Our results suggest that social networks in the participating organisations may have contributed to some of this variation. Furthermore, we found evidence that project managers tended to modify their own social network to advance their QI initiative from one stage of implementation to the next. In the

following, we present how the QI initiatives progressed through the different stages of implementation, highlighting the role played by network structures in these transitions.

Exploration to installation

During the initial stage of exploration, project managers examined their organisations' needs and available resources. A consistent pattern emerged among all participants, whereby high **betweenness centrality** facilitated exploratory activities by improving the flow of information across organisational units. In contrast, participants who reported low betweenness centrality in the survey encountered challenges in transferring information between different units of their organisations. For instance, one participant expressed having difficulties in adequately defining organisational needs and consequently struggling to progress beyond the exploration stage:

"*The difficulty for me was actually to think about what to do – in other words, what the initiative is, […] and to understand what is actually important for us right now. And yes, this took me a very, very long time and it basically only became clear towards the end [of the QIC].*" *(P1 t1)*

Participants who were aware of this need for high betweenness centrality but lacked it actively sought strategic connections: Whereas one project manager sought to bridge multiple structural holes by tapping into a newly established occupational health advisory board that had members from different organisational units, other participants singled out specific individuals who served as gatekeepers across the organisation:

"*In each organisation, it's very, very important to figure out who needs to be involved so that it's ultimately sustainable and can be implemented. In our case, this certainly includes general management and quality management. In my role, I have to initiate contact with the care home managers or nursing service managers of the individual facilities and convince them. They are the ones who have to help implement the initiative.*" (*P7 t1*)

Betweenness centrality appeared equally important for embedding new QI initiatives within existing organisational structures. For instance, one project manager planned to integrate workplace health and well-being nudges into an internal mobile device app but was unsuccessful

in communicating his or her needs to the technical staff. This example highlights how some participants were unable to modify their network despite repeated efforts. When asked what was needed to progress with the initiative, the project manager responded:

"*Simply an openness, for people to say: Okay, we're going to get this wellness program up and running – this is not about me personally now, but about workplace health. I think that the IT people need to be informed at an early stage in planning to make this possible. To be honest, I don't know whether the app will end up being fit for purpose.*" (*P2 t1*)

We observed that high **network density** exacerbated this effect. Most of the project managers whose network position entailed no betweenness centrality, but high network density appeared to be isolated in "echo chambers" in which redundant information and old beliefs were amplified. One project manager in a highly dense network related how the network's collective memory of past unsuccessful initiatives undermined the credibility of a new attempt at implementation. However, the participant reported that this effect could be overcome by collaborating with external partners, effectively introducing fresh ideas into the network.

"[One barrier was] acceptance by staff members that something would actually happen, along the lines of: 'Oh, this has been tried a hundred times, and nothing ever came of it. […] [A lack of] acceptance among staff has now been turned into hope through the involvement of this external company, which is doing a really great job." (*P5 t1*)

The advantage of social networks with high betweenness centrality over those with high network density was especially apparent for QI initiatives with an organisation-wide scope. In contrast, the few project managers who initiated small-scale QI initiatives were able to progress without any betweenness centrality. In these cases, it appeared necessary for the staff members directly involved in the initiative to be "willing to contribute their own ideas, wishes, and thoughts" (*P8 T_2*). We also found discontinuities where implementation was interrupted early on by project managers' inability to initiate betweenness centrality. In one organisation, for instance, implementation did not progress beyond the exploration stage because the process of designing an appropriate intervention failed due to low betweenness centrality.

Installation to initial implementation

During the installation stage, many project managers focused on setting up accountability structures, funding streams, and necessary infrastructure within the organisation to implement their respective QI initiatives. Our findings suggest that **network density** facilitated progress during this stage by fostering trust and shared sense-making among staff. Several project managers emphasized that the pursuit of common goals contributed to the progress of installation activities. For example, one project manager in a highly dense network listed factors that were helpful during this stage:

"*Definitely the support and freedom that was given to us. This attitude of: You can do this – we trust you. That was a very important point.*" (*P4 t1*)

Furthermore, we found that the creation of working groups and decision boards for QI management increased network density, serving as mechanisms to bring formerly distant nodes together, resulting in increased connectivity and collaboration. This was evident from the data we obtained from the network surveys and interviews conducted throughout the implementation process. One project manager reflected on how he or she generated more interest and motivation for a QI initiative by reinforcing engagement among colleagues:

"*[One hurdle was] the lack of motivation among staff, who were all exhausted from COVID and didn't really feel like working – and now another initiative? But when they realized it could also be fun, that they could help shape things, and through the motivation that other colleagues and I gave them, it worked out quite well after all.*" (*P3 t1*)

During the installation stage, **degree centrality** also appeared to become relevant. While we found no differences in access to financial resources between project managers with higher or lower degree centrality, the project managers themselves perceived considerable variations in the time allocated to their initiative depending on this characteristic. Specifically, we found that those with high degree centrality found it easier to prioritize tasks related to their QI initiative over their daily work. One project manager expressed this by stating:

"*In terms of time, I expressed my needs clearly, and then I was given the time. That was very, very generous. I only said once that I simply couldn't do it and that I needed more time, and then it was given to me.*" (*P5 t1*)

In contrast, project managers with low degree centrality, operating from the periphery of their organisations, encountered difficulties in exerting influence regarding the importance of their QI initiative. They often referred to problems with allocating sufficient time for the initiative. One project manager highlighted this issue by stating:

"*[Health and well-being in the workplace] is a topic where you can't just assume you'll have plenty of time for it. You need time to implement it, to reflect on it, and, where necessary, to incorporate feedback. And workplace well-being programs are often something that happens on the sidelines.*" (*P1 t1*)

We again observed discontinuities in implementation in cases where a project manager's initial enthusiasm for a QI initiative, fostered in the collaborative setting of the QIC, failed to transfer to other members within their organisation. One project manager ultimately abandoned his or her QI initiative between the two data collection time points, indicating that it had been hindered from progressing further due to a lack of solidarity from members of his or her social network.

Initial implementation to full operation

During the initial implementation stage, project managers focused on scaling the use of their respective QI across their entire organisation. Once again, **betweenness centrality** played a crucial role in most organisations, with high betweenness centrality facilitating progress by enabling better information flow. However, most project managers first needed to establish higher betweenness centrality by connecting with distant units within their respective organisations. Several project managers actively disseminated information about their QI initiative due to a lack of uptake beyond their immediate circle. One project manager shared his or her experience, stating:

"*For example, I visited the nutrition therapy team and presented our entire program to them again. And they didn't even know, for example, that we had a swimming pool – that's really astonishing. So I personally went with them to the swimming pool and showed them our premises.*" (*P5 t_2*)

At the same time, **network density** that was generated during the installation stage played an equally important role in facilitating progress towards full operation. The within-group cohesion that resulted from the network density helped maintain a core team to support ongoing and expanding QI efforts. One project manager highlighted the positive impact of network density on cooperation among staff, stating:

"*Communication with staff was very important. And it was also nice to see, once again, that everyone deals with things very openly and honestly and that we were really able to inspire the care home management and nursing staff. […] So the employees have become more aware, and many are now taking workplace well-being more seriously.*" (*P7 t_2*)

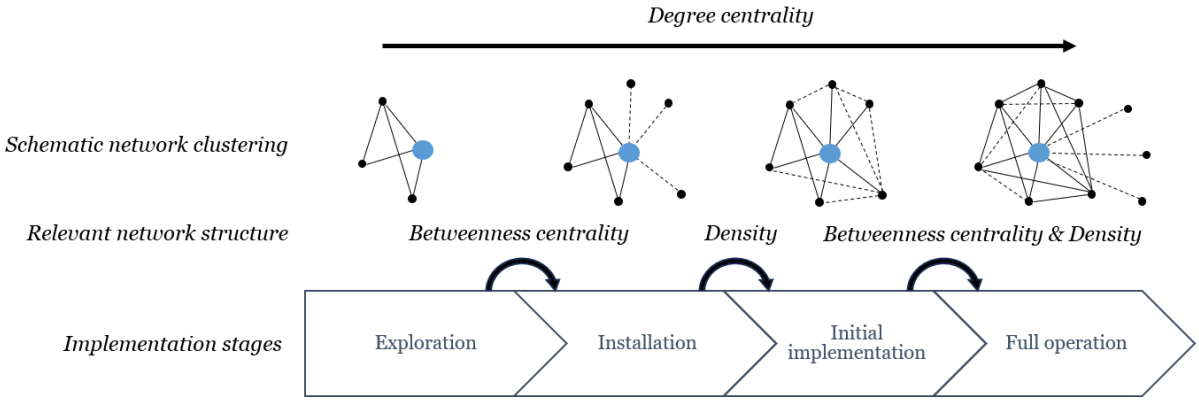
Network clustering within organisations through QIC participation

Throughout the implementation process, all project managers experienced an expansion of their social network in their organisation following QIC participation, as indicated by an increase in **degree centrality**:

"*[I'm] now in touch with significantly more people than would be the case for, let's say, a normal employee. [I'm] in touch with all parts of the organisation, be it the nursing homes, the practices, the services within the hospital. It's very nice and also very pleasant to have more frequent contact with the pertinent individuals there.*" (*P2 t_2*)

However, not all QI initiatives were able to progress through all four stages. As a result, we observed only a few instances of full implementation. This was particularly evident in the relatively high number of project managers who either left their organisation after participating in the QIC or discontinued their QI initiatives, as reflected in the lower number of interviewees during t_2. When we connected our findings across the different stages of implementation, we observed how

different configurations of structural network characteristics were needed to progress through the implementation stages. Moreover, we observed that project managers whose QI initiatives progressed to more advanced stages of implementation formed *ad hoc* arrangements of colleagues who were passionate about the initiative. We refer to these ad hoc groups of colleagues in a project manager's social network as a "QI cluster". As illustrated in Figure 2-2, these QI clusters consisted of formerly unconnected colleagues who were from various parts of the organisation (*betweenness centrality*) and developed very frequent interactions (*network density*). Once a QI cluster was formed in an organisation, the progress of implementation slowed unless further betweenness centrality was achieved to transition to the full operation stage.



Schematic representation of network clustering occurring during the implementation process. Blue: Focal implementer (QI project manager); solid lines: existing network ties; dashed lines: new network ties.

Figure 2-2 Network clustering occurring over multiple stages of implementation.

This observation highlights how project managers' activities and achievements during earlier stages of the implementation process can modify the implementation context for subsequent stages. If betweenness centrality is lacking in the early stages but the transition to the next stage of implementation still succeeds, the limited inclusion of colleagues across the organisation may have negative repercussions for the full operation of the initiative. One project manager describes this phenomenon, stating:

"*We wanted to do [the QI initiative] in a way that encompassed all our facilities, particularly focusing on achieving sustainability. In the past, we carried out initiatives where we conducted*

staff surveys, but [the implementation] varied across different facilities, and some did not fully follow through. That's why it was crucial for us to come together and view this as a management responsibility." (*P1 t1*)

Discussion

Despite the increasing number of QI methods developed in collaborative cross-organisational formats, there remains a gap in understanding how these are implemented locally or why they so frequently fail to achieve full implementation (Aunger et al, 2021; Strating & Nieboer, 2013; Nembhard 2012). We therefore conducted a qualitative process study to examine how QI project managers' social networks influence the local implementation of initiatives developed through a QIC. Our findings support the assertion that interpersonal relations in organisations are important for QI implementation (Coles et al., 2020). However, we found that the optimal structure of a social network varies across different stages of implementation as project managers encounter varying needs in the evolving implementation context. The same network structure may thus facilitate or hinder the progress of a QI initiative depending on the stage of implementation in which it is situated.

Consistent with the literature highlighting the benefits of having well-connected opinion managers delivering QI implementation (Bunger et al., 2023), we found that degree centrality facilitates progress from initial to full operation by maximizing social influence. In contrast, network density hinders progress during the early stages of implementation by isolating actors from other organisational units (Adler & Kwon, 2002). However, higher network density becomes necessary during later stages of implementation to bring about and sustain the required behavioural changes among members of participating organisations. This finding aligns with research indicating that higher network density strengthens commitment to agreed-upon behaviour and discourages deviance from these actions (Meltzer et al., 2010). Additionally, higher betweenness centrality was found to be important during phases of broad knowledge acquisition, probably because it gives access to distributed organisational knowledge (Newell, Tansley & Huang, 2004).

We also observed that project managers appeared to modify their social networks to advance their respective QI interventions from one stage of implementation to the next. This suggests that lower-level interactions, directed at making implementation work "on the ground" recursively constitute higher-level interactions of establishing new network connections (Cloutier & Langley, 2020). Such "feedback loops" can lead to the emergence of clusters of individuals who are passionate about and thus supportive of the implementation of the QI initiative within an organisation over time. These clusters emerge because of a sequential process involving betweenness-building and density-building activities, wherein a project manager fosters a growing number of interconnected ties in his or her organisation.

There is evidence that building groups or clusters of supportive individuals is one of the most effective networking strategies to facilitate implementation because it brings together influential individuals who have a common goal (Bunger et al., 2023). Importantly, our results highlight that this clustering phenomenon occurs dynamically through needs-driven relationship building, even when the QIC curriculum itself does not include networking training for QI project managers. By highlighting the importance of social networks in individual organisations participating in QICs, our findings are relevant for healthcare managers seeking to improve quality of care. Overall, we found that an inability to translate QIC participation into even minimal progress of a QI initiative tended to occur in organisational environments in which network building was perceived as inhibited. In contrast, organisations in which QI initiatives progressed furthest were characterized by environments that enabled project managers to direct their networking efforts towards purposeful connections.

When providing QI project managers with opportunities to establish connections across organisational units, it would be wise for organisations to anticipate the project managers' networking needs along the entire implementation pathway. This knowledge could lead to more effective efforts to improve the quality of care. We hope that our study will stimulate further research on the conditions that need to be met by social networks at different stages of

implementation to inform the design of future QI initiatives and collaborative curricula for developing them.

Limitations

Our study is subject to several important limitations, each of which offers opportunities for further research. First, the QIC case examined in this study involved the recruitment of individual project managers from each organisation. Further research is needed to explore how the role of social networks might differ in cases where multiple staff members from each organisation participate in a QIC. This is of relevance given evidence that social networks differ in structure depending on the role of the professional in question (Tasselli, Zappa & Lomi, 2020). Moreover, understanding network structures and the extent to which team members' own networks overlap and complement each other would provide valuable insights. Second, we only gained access to participants once the active QIC phase had been completed, which prevented us from prospectively collecting data from the early stages of implementation. While this means that some of our findings are subject to recall bias, our use of extensive data triangulation may have helped mitigate this issue. Lastly, we focused only on three specific structural characteristics of networks of one individual within an organisation. While our choice of characteristics was guided by the literature, it must be acknowledged that the number of network descriptors and measurement approaches in this domain is vast. Researchers seeking to elaborate upon our findings may therefore wish to explore alternative mapping techniques to uncover additional network conditions or direct their inquiry at sociocentric networks, which consider entire networks without focusing on an individual.

Practical implications

Our study supports the view that there is no "one size fits all" approach to implementing QI initiatives, even when these are developed by organisations participating in the same QIC (Krein et al., 2010). Instead, our results highlight the importance of recognizing that actors are situated in structurally diverse social networks with variable networking opportunities. Beyond acknowledging social networks as important contextual factors, strategies for implementing QI initiatives should therefore equip project managers with the awareness and skills to foster degree

centrality, network density, and betweenness centrality at the stages of the implementation process at which these are most needed. Such targeted training can particularly benefit larger organisations with rigid hierarchies, where the formation of clusters of individuals supporting the implementation of the QI initiative across organisational units may be challenging. By differentiating between the different social network conditions of the stage of implementation at which a QI initiative is situated, implementation strategies can be tailored more effectively. Shelton et al. (2019) highlight general strategies for doing so, such as identifying opinion leaders, activating new ties, and making structural changes to existing networks. Strategies like these can be flexibly combined to facilitate transitions across multiple stages of the implementation process.

Furthermore, our findings reinforce the importance of the local implementation context. While collaborative formats that involve multiple organisations in the design of QI initiatives are valuable for distributing generalizable scientific evidence (Batalden & Davidoff, 2007) and promoting improvements through accountability and the sharing of best practices (Øvretveit et al., 2002), we observed that the progress of implementation among organisations participating in the same QIC varied considerably. Each participating organisation embarks on an individual implementation journey within its unique network context. Therefore, organisations seeking to improve care should pay particular attention to their local implementation environment, even when developing a QI initiative in a collaborative setting such as a QIC.

Conclusion

Our qualitative process study examined the influence of social networks in organisations on the multistage pathway from the training of individual QI project managers to the local implementation of QI initiatives developed through QICs. We found that three structural characteristics of social networks – degree centrality, network density, and betweenness centrality – each fulfilled specific conditions for implementation and therefore facilitated or hindered implementation depending on the stage of implementation at which a QI initiative was situated. Additionally, our study revealed the gradual formation of clusters of individuals supporting QI implementation as a result of networking activities that were undertaken in response to the specific

needs of a QI initiative during each implementation stage. These findings highlight the need for a better understanding of the local implementation context in collaborative QI formats to ensure effective implementation.

Bibliography

Adler, P. S. & Kwon, S.-W. 2002. Social Capital: Prospects for a New Concept. *Academy of Management Review*, *27*(1): 17–40. DOI: 10.5465/amr.2002.5922314

Auerbach, A. D., Landefeld, S. & Shojania, K. G. 2007. The Tension between Needing to Improve Care and Knowing How to Do It. *The New England Journal of Medicine*, *357*(6): 608–613. DOI: 10.1056/NEJMsb070738

Aunger, J.A., Millar, R., Greenhalgh, J., Mannion, R., Rafferty, A.M. & McLeod, H. 2020: Why do some inter-organisational collaborations in healthcare work when others do not? A realist review. *Systematic Reviews, 10*(82): 1-22. DOI: 10.21203/rs.3.rs-58882/v1.

Batalden, P. B. & Davidoff, F. 2007. What is "quality improvement" and how can it transform healthcare? *Quality & safety in healthcare*, *16*(1): 2–3. DOI: 10.1136/qshc.2006.022046

Boland, R. J. & Tenkasi, R. V. 1995. Perspective Making and Perspective Taking in Communities of Knowing. *Organisation Science*, *6*(4): 350–372. DOI: 10.1287/orsc.6.4.350

Brands, R. A., Menges, J. I. & Kilduff, M. 2015. The Leader-in-Social-Network Schema: Perceptions of Network Structure Affect Gendered Attributions of Charisma. *Organisation Science*, *26*(4): 1210–1225. DOI: 10.1287/orsc.2015.0965

Bunger, A. C. & Lengnick-Hall, R. 2018. Do learning collaboratives strengthen communication? A comparison of organisational team communication networks over time. *Healthcare management review*, *43*(1): 50–60. DOI: 10.1097/HMR.0000000000000120

Bunger, A. C., Yousefi-Nooraie, R., Warren, K., Cao, Q., Dadgostar, P. & Bustos, T. E. 2023. Developing a typology of network alteration strategies for implementation: a scoping review and iterative synthesis. *Implementation science : IS*, *18*(1): 10. DOI: 10.1186/s13012-023-01266-3

Burt, R. S. 1987. Social Contagion and Innovation-Cohesion Versus Structural Equivalence. *The American Journal of Sociology*, *92*(6): 1287–1335. DOI: 10.1086/228667

Burt, R. S. 2000. The network structure of social capital. *Research in organisational behavior*, *22*: 345–423. https://ebookcentral.proquest.com/lib/kxp/detail.action?docID=305650

Chambers, D., Glasgow, Russell, E. & Stange, K. C. 2013. The dynamic sustainability framework: addressing the paradox of sustainment amid ongoing change. *Implementation science : IS*, *8*(117). DOI: 10.1186/1748-5908-8-117

Cloutier, C. & Langley, A. 2020. What Makes a Process Theoretical Contribution? *Organisation Theory*, *1*(1), 263178772090247. DOI: 10.1177/2631787720902473

Coles, E., Anderson, J., Maxwell, M., Harris, F. M., Gray, N. M., Milner, G. & MacGillivray, S. 2020. The influence of contextual factors on healthcare quality improvement initiatives: a realist review. *Systematic reviews*, *9*(1): 94. DOI: 10.1186/s13643-020-01344-3

Creswell, J. W. & Poth, C. N. 2016: Qualitative Inquiry and Research Design: Choosing Among Five Approaches: SAGE Publications.

Dückers, M. L. A., Wagner, C., Vos, L. & Groenewegen, P. P. 2011. Understanding organisational development, sustainability, and diffusion of innovations within hospitals participating in a multilevel quality collaborative. *Implementation science : IS*, *6*(18). DOI: 10.1186/1748-5908-6-18

Fixsen, D. L., Naoom, S. F., Blase, K. A., Friedman, R. M. & Wallace, F. 2005. *Implementation Research: A Synthesis of the Literature*. Tampa, Florida. University of South Florida.

Glegg, S. M. N., Jenkins, E. & Kothari, A. 2019. How the study of networks informs knowledge translation and implementation: a scoping review. *Implementation science : IS*, *14*(1): 34. DOI: 10.1186/s13012-019-0879-1

Granovetter, M. S. 1973. The Strength of Weak Ties. *American Journal of Sociology*, *78*(6): 1360–1380. DOI: 10.1086/225469

Hill, J. E., Stephani, A.-M., Sapple, P. & Clegg, A. J. 2020. The effectiveness of continuous quality improvement for developing professional practice and improving healthcare outcomes: a systematic review. *Implementation Science*, *15*(1): 23. DOI: 10.1186/s13012-020-0975-2

Institute for Healthcare Improvement. 2003. *The Breakthrough Series: IHI's Collaborative Model for Achieving Breakthrough Improvement* (Innovation Series 2003 Nr. 3). Cambridge, MA. Institute for Healthcare Improvement.

Krein, S. L., Damschroder, L. J., Kowalski, C. P., Forman, J., Hofer, T. P. & Saint, S. 2010. The influence of organisational context on quality improvement and patient safety efforts in infection prevention: a multi-center qualitative study. *Social science & medicine (1982)*, *71*(9): 1692–1701. DOI: 10.1016/j.socscimed.2010.07.041

Langley, A. 2007. Process thinking in strategic organisation. *Strategic Organisation*, *5*(3): 271–282. DOI: 10.1177/1476127007079965

Langley, A., Smallman, C., Tsoukas, H. & van de Ven, A. H. 2013. Process Studies of Change in Organisation and Management: Unveiling Temporality, Activity, and Flow. *Academy of Management Journal*, *56*(1): 1–13. DOI: 10.5465/amj.2013.4001

Macik-Frey, M., Quick, J.C., & Nelson, D.L. 2007. Advances in Occupational Health: From a Stressful Beginning to a Positive Future. *Journal of Management 33*(6): 809–840. DOI: 10.1177/0149206307307634.

Mascia, D., Pallotti, F. & Dandi, R. 2018. Determinants of knowledge-sharing networks in primary care. *Healthcare management review*, *43*(2) 104–114. DOI: 10.1097/HMR.0000000000000139

McCarty, C. 2002: Structure in personal networks. *Journal of Social Structure* 3 (1).

Mehra, A., Borgatti, S. P., Soltis, S., Floyd, T., Halgin, D. S., Ofem, B. & Lopez-Kidwell, V. 2014. Imaginary Worlds: Using Visual Network Scales to Capture Perceptions of Social Networks. In D. J. Brass, G. Labianca, A. Mehra, D. S. Halgin & S. P. Borgatti (Hrsg.), *Research in the*

Sociology of Organisations. Contemporary Perspectives on Organisational Social Networks (Bd. 40, S. 315–336). Emerald Group Publishing Limited. DOI: 10.1108/S0733-558X(2014)0000040016

Meltzer, D., Chung, J., Khalili, P., Marlow, E., Arora, V., Schumock, G. & Burt, R. 2010. Exploring the use of social network methods in designing healthcare quality improvement teams. *Social science & medicine (1982)*, *71*(6): 1119–1130. DOI: 10.1016/j.socscimed.2010.05.012

Nembhard, I. M. 2012. All teach, all learn, all improve? the role of interorganisational learning in quality improvement collaboratives. *Healthcare management review*, *37*(2): 154–164. DOI: 10.1097/HMR.0b013e31822af831

Newell, S., Tansley, C. & Huang, J. 2004. Social Capital and Knowledge Integration in an ERP Project Team: The Importance of Bridging AND Bonding. *British Journal of Management*, *15*(S1): 43–57. DOI: 10.1111/j.1467-8551.2004.00399.x

Øvretveit, J., Bate, P., Cleary, P., Cretin, S., Gustafson, D., McInnes, K., McLeod, H., Molfenter, T., Plsek, P., Robert, G., Shortell, S. & Wilson, T. 2002. Quality collaboratives: lessons from research. *Quality & safety in healthcare*, *11*(4): 345–351. DOI: 10.1136/qhc.11.4.345

Perry-Smith, J. E. & Mannucci, P. V. 2017. From Creativity to Innovation: The Social Network Drivers of the Four Phases of the Idea Journey. *Academy of Management Review*, *42*(1): 53–79. DOI: 10.5465/amr.2014.0462

Saldaña, J. 2013. *The coding manual for qualitative researchers* (2nd ed.). Sage.

Shea, C. M., Turner, K., Albritton, J. & Reiter, K. L. 2018. Contextual factors that influence quality improvement implementation in primary care: The role of organisations, teams, and individuals. *Healthcare management review*, *43*(3): 261–269. DOI: 10.1097/HMR.0000000000000194

Shelton, R. C., Lee, M., Brotzman, L. E., Crookes, D. M., Jandorf, L., Erwin, D. & Gage-Bouchard, E. A. 2019. Use of social network analysis in the development, dissemination,

implementation, and sustainability of health behavior interventions for adults: A systematic review. *Social science & medicine (1982)*, *220*: 81–101. DOI: 10.1016/j.socscimed.2018.10.013

Strating, M. H. & Nieboer, A. P. 2013. Explaining variation in perceived team effectiveness: results from eleven quality improvement collaboratives. *Journal of clinical nursing 22*(11-12): 1692–1706. DOI: 10.1111/j.1365-2702.2012.04120.x

Sun, S. 2011. Meta-analysis of Cohen's kappa. *Health Services and Outcomes Research Methodology*, *11*(3-4): 145–163. DOI: 10.1007/s10742-011-0077-3

Tasselli, S., Zappa, P. & Lomi, A. 2020. Bridging Cultural Holes in Organisations: The Dynamic Structure of Social Networks and Organisational Vocabularies Within and Across Subunits. *Organisation Science 31*(5): 1292–1312. DOI: 10.1287/orsc.2019.1352

Tenkasi, R. V. & Chesmore, M. C. 2003. Social Networks and Planned Organisational Change. *The Journal of Applied Behavioral Science*, *39*(3): 281–300. DOI: 10.1177/0021886303258338

Yin, R. K. 2014. *Case Study Research Design and Methods* (5th edition). Sage. DOI: 10.3138/cjpe.30.1.108

Zamboni, K., Baker, U., Tyagi, M., Schellenberg, J., Hill, Z. & Hanson, C. 2020. How and under what circumstances do quality improvement collaboratives lead to better outcomes? A systematic review. *Implementation science, 15*(1). DOI: 10.1186/s13012-020-0978-z

Paper 3

Concordance in Clinical Evidence Submissions to the FDA and EMA for Gene and Cell Therapies

---

Sandra Gillner, M.A. M.Sc.[1,2], Magdi Elsallab, MD PhD[3,4], Florence Bourgeois, MD MPH[3]

[1] KPM Center for Public Management, University of Bern, Freiburgstr. 3, 3010 Bern, Switzerland

[2] Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel), Freiburgstr. 3, 3010 Bern, Switzerland

[3] Harvard-MIT Center for Regulatory Science, Harvard Medical School, Boston, MA

[4] Cellular Immunotherapy Program, Mass General Cancer Center, and Department of Medicine, Harvard Medical School, Boston, MA

This is the originally submitted version of the article published under the following link: https://doi.org/10.1001/jamainternmed.2024.7569

Acknowledgements and funding: This research collaboration has been made possible by a Doc.Mobility grant awarded and funded by the University of Bern. At the time of submission of this dissertation, this paper is presently under review at a peer-reviewed academic journal.

Abstract

Importance: Gene and cell therapies (GCTs) are predicted to significantly expand pharmaceutical options for rare diseases and conditions with unmet clinical needs, though substantial barriers remain related to the complexity of product development. Efforts to harmonise regulatory activities across agencies could increase efficiencies and reduce time and cost to availability of GCTs.

Objective: To evaluate concordance in the submission of GCT approval packages to the FDA and EMA in terms of timing of application submission and reporting of clinical trial data.

Design: Cross-sectional analysis of GCT applications submitted to the FDA and EMA through October 3, 2023.

Setting: Approved products were identified from agency databases and data on clinical trial reporting extracted from the approval documents.

Participants: GCTs and corresponding applications for original and supplemental indications approved by both the FDA and EMA.

Main Outcomes and Measures: We determined differences in the time between application submission dates to the FDA and EMA, review duration, and time between approval dates. Concordance in clinical trial data reporting was measured as the number of applications reporting on the same primary clinical trials and presenting matching values for four key primary clinical trial characteristics (sample size, primary endpoint, comparator type, and efficacy outcome).

Results: The study sample included 15 GCTs, corresponding to 20 applications. Sponsors submitted applications a median of 4.1 (IQR -12.2,5.0) weeks earlier to the FDA (p=0.5135) and the median review duration was 20.9 weeks shorter for the FDA (p=0.0001). Overall, products were approved a median of 23.1 weeks (IQR 49.0,4.5) weeks earlier by the FDA (p=0.1536). 17 applications reported on the same primary clinical trials, and 4 of 17 primary trials matched on key clinical trial characteristics. Overall, there was concordance in the reporting of primary clinical trial data for 4 (20%) applications between the FDA and EMA.

Conclusions and Relevance: There are substantial differences in the timing of regulatory activities and reporting of clinical trial data for GCT applications submitted to the FDA and EMA. These findings highlight potential opportunities for nascent harmonisation efforts to increase alignment in regulatory reviews for GCT products across agencies.

Introduction

Gene and cell therapies (GCTs) are predicted to significantly expand pharmaceutical options for the treatment of rare diseases and conditions with unmet clinical needs (Schneier et al., 2010). While only few products have been approved in the US and in Europe so far (Elsallab et al., 2020; Barkholt et al., 2019; Bravery, Ball, & Robinson, 2019; de Wilde et al., 2018; Iglesias-Lopez et al., 2021), the number of GCT therapies is expected to grow substantially in the coming years, with close to 4,000 GCTs in the development pipeline globally (American Society of Gene and Cell Therapy, 2024). However, regulatory requirements present a potential bottleneck to commercial availability of new GCTs across jurisdictions due to the regulatory complexity and associated costs of developing these products (ten Ham et al., 2018).

Harmonisation in regulatory requirements across regulatory agencies may support timelier access by eliminating costs and inefficiencies arising from duplicated evidence dossiers and parallel assessment by multiple agencies (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2024a). Acknowledging the need for greater regulatory convergence, the U.S. Food and Drugs Agency (FDA) recently announced the pilot program Collaboration on Gene Therapies Global Pilot (CoGenT), promoting regulatory harmonisation for the assessment of GCTs through coordination of GCT submission reviews between the FDA, European Medicines Agency (EMA), and other regulatory agencies (FDA, 2024a). Importantly, the proposed harmonisation calls for alignment of the evidence submitted by sponsors to collaborating regulatory agencies. Considering these current efforts to increase harmonisation, understanding how drug sponsors currently approach parallel submissions of GCT approval applications to different agencies is crucial to fully define areas in need of alignment and assess the eventual impact of this regulatory initiative.

In this study, we present an assessment of current practices for GCT application submissions to the FDA and EMA. The analysis compares the evidence submitted by sponsors to the FDA and EMA, focusing on the timing of submission of application packages and the reporting of clinical trial data for GCT products approved in both the US and Europe.

Methods

Product identification and data sources

All GCT products approved by the FDA were identified from the FDA's Office of Tissues and Advanced Therapies website (FDA, 2024b). For each product, all FDA approval documents, including Summary Basis for Regulatory Action (SBRA) reports, clinical and statistical reviews, and approval letters, are publicly available on the site. The EMA publishes a list of GCT products approved by the EMA, along with the European Public Assessment reports (EPARs), which contain information on the clinical trials supporting the approval (EMA, 2024), as well as "Summary of Product Characteristics" which detail labelling for each product. We included all original GCT applications and applications for supplemental therapeutic indications approved by the FDA and EMA as of October 3, 2023. Applications only involving changes to the indication for the product line of therapy (e.g., from third line to second line) were excluded if the application did not include a unique clinical trial supporting this new indication.

Data extraction and definitions

Applications for each product were reviewed to identify product characteristics, timelines for regulatory activities, and characteristics of the primary and secondary clinical trials. Data classifications were conducted by one investigator (SG) and validated by a second investigator (ME). Disagreements were resolved through discussion with a third investigator (FB).

Product Characteristics

Definitions of cell-based therapies and tissue-engineered products differ between the FDA and EMA, with certain therapies considered cell-based therapies by the FDA but classified as tissue-engineered products by the EMA. For our purposes, we combined the two groups as "cell-based therapy".

To standardise product indications between the two agencies, we mapped the indications for each product to the "Preferred Term" in the Medical Dictionary for Regulatory Activities (MedDRA)

hierarchy (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2024b). MedDRA offers a system of standardised international medical terminology regularly used by both the FDA and EMA. We then categorised the therapeutic area of each GCT indication based on the primary "System Organ Class" of the corresponding Preferred Term in the MedDRA hierarchal clustering.

Timelines for regulatory activities

Application submission dates and product approval dates were obtained from regulatory review and approval documents, as well as the EMA product websites. The application review duration was calculated as the number of weeks between the date of submission and approval for each product. Under EMA, these review durations include clock stop periods, which EMA can invoke after 120 and again after 180 days into the evaluation process. During this period, appraisal of the submitted evidence pauses until the applicant submits new data or responds to a list of questions or issues. In addition, we extracted information about withdrawn products, including reason and date of withdrawals, from the FDA's website and the EMA's public statements on product withdrawals listed on the respective product websites.

Both the FDA and EMA use orphan designations and certain expedited regulatory pathways, including breakthrough designation by the FDA and PRIME designation by the EMA. Where applicable, we extracted the dates on which orphan, breakthrough, or PRIME designations were granted by the FDA and EMA.

Clinical trial characteristics

For each application package, information on the primary and secondary clinical trials were extracted. Primary trials were defined as the trials used as the basis for a decision on the clinical efficacy and safety of a product and were specified as the primary source of evidence in SBRAs and as "main studies" in the EPARs. Secondary trials were defined as other studies that provide supporting data, listed as "supportive studies" in SBARs and EPARs.

For each clinical trial, data were extracted on trial phase, multicentre status, randomisation status, blinding, sample size, primary endpoint, comparator type, and primary efficacy outcome (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2021). The sample size of a study was defined as the evaluable efficacy population used to determine treatment effects by the regulators. This number differed from the number of participants enrolled or those treated, if the participants did not meet certain criteria (e.g. genetic predisposition or availability of follow-up data) and were excluded by the regulator in their evidence assessment. Primary endpoints were categorised as clinical outcomes, clinical scales, or surrogate endpoints based on previous classifications (Clement et al., 2009; Downing et al., 2014). Clinical endpoints assess patient survival or function, clinical scales quantify clinical patient-reported symptoms, and surrogate endpoints approximate clinical benefit based on biomarkers. Trials may either be single- or multi-arm trials, depending on the inclusion of a comparator group. For multi-arm trials, comparators were classified as active comparators, placebo, external or historical controls, or no treatment, based on definitions provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2021), which both FDA and EMA comply with. Lastly, we recorded the results of the primary efficacy outcome. Efficacy outcomes provide the numerical value of the primary endpoint recorded on the date of data cut-off. If several cut-off dates were mentioned in the application documents, we selected the latest cut-off date and corresponding efficacy outcome.

Matching of GCTs, clinical trials, and trial characteristics

To enable a comparison of clinical evidence submissions to FDA and EMA, we identified all GCTs approved by both the FDA and EMA along with the respective original and supplemental application packages. GCT applications were matched across the two regulatory agencies based on the treatment indication.

For each application package, we matched primary and secondary clinical trials using the sponsor-assigned trial ID and NCT number, noting whether application packages included the same set of trials. For matched primary trials, we compared the following four clinical trial characteristics:

sample size, primary endpoint, comparator type, and efficacy outcome. We did not compare blinding, randomisation, or trial phase, as no differences in reporting would be anticipated for these characteristics. For the secondary trials, we determined whether the same trials were submitted to each agency.

Statistical analysis

We used descriptive statistics to characterise the GCT products and application packages. We tested normal distribution of main variables and residuals via the Shapiro-Wilk test. We determined median differences in submission dates to the FDA and EMA by application submission year and ran a linear regression to determine whether this difference changed over time. We determined the median review durations for application packages submitted to the FDA and EMA. We determined median differences in approval dates to the FDA and EMA by application approval year and ran a linear regression to determine whether this difference changed over time. For matched application packages, we determined the percentage that had concordant clinical evidence reporting, defined as submission of the same set of primary and secondary trials and the same values for the four clinical trial characteristics of interest for all primary trials. Due to the non-parametric nature of our data and matching observations for each application package and trial between FDA and EMA, we used a Wilcoxon signed-rank test to test significance in differences between submission dates, review durations, approval dates, and reported sample sizes. Statistical analyses were conducted in R Studio (version 4.3.1) and Graphpad prism (version 10.0.0). For all analyses, a 2-tailed p-value ≤ 0.05 was considered statistically significant.

Results

Study cohort

There were 24 GCT products approved by the FDA and 25 by the EMA, with 15 approved by both regulatory agencies and comprising our study cohort (Table 3-1). Thirteen (87%) were gene therapy products and two (13%) cell-based therapies. The 15 GCT products corresponded to a total of 20 matched applications, with 12 GCTs with a single original application, one with an original and a

supplemental application, and two with an original and two supplemental applications. Most applications included an indication with an orphan designation (18 [90%] for FDA and 17 [85%] for EMA), with difference between the agencies stemming from a gene therapy (talimogene laherparepvec) that received orphan designation by the FDA but not the EMA. Use of expedited approval pathways was prevalent for both agencies, with 16 (80%) product applications granted breakthrough designation by FDA and 12 (60%) PRIME designation by EMA. Neoplasms were the most frequently represented therapeutic area, comprising 13 (65%) approved GCT indications.

Table 3-1 Study cohort of gene and cell-based therapies approved by the FDA and EMA.

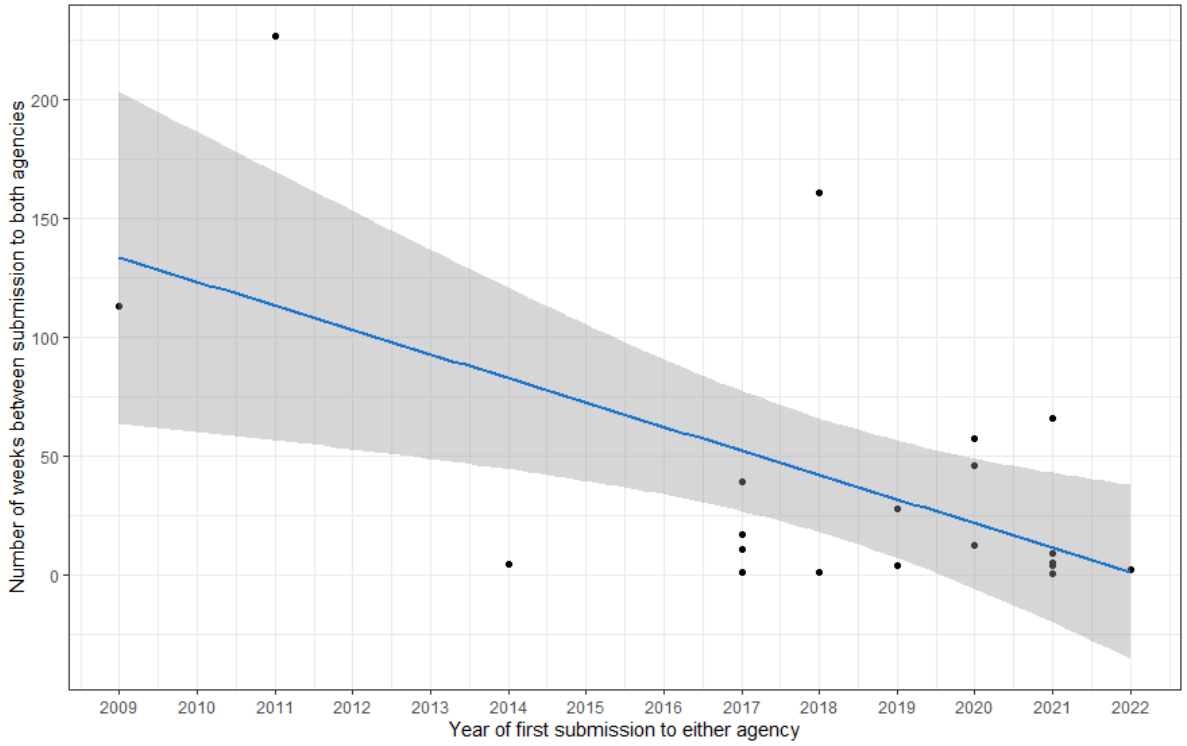
	Product characteristics	**GCT products, N (%) (N = 15)**	**Matched application packages, N (%) (N = 20)**
Product type	Gene therapy	13 (87)	18 (90)
	Cell-based therapy	2 (13)	2 (10)
Orphan designation			
	FDA	13 (87)	18 (90)
	EMA	12 (80)	17 (85)
Use of expedited regulatory pathway			
	Breakthrough (FDA)	12 (80)	16 (80)
	PRIME (EMA)	11 (73)	12 (60)
Disease area	Neoplasms	8 (53)	13 (65)
	Blood and lymphatic system disorders	3 (20)	3 (15)
	Musculoskeletal and connective tissue disorders	2 (13)	2 (10)
	Metabolism and nutrition disorders	1 (7)	1 (5)
	Eye disorders	1 (7)	1 (5)

Timelines for regulatory activities between FDA and EMA

Sponsors submitted 14 (70%) applications to the FDA prior to the EMA and 6 (30%) to the EMA first (Figure 3-1). On average, the FDA received applications a median of 4.1 (IQR, -12.2,5.0) weeks earlier than EMA (p=0.51). Submission to the FDA and EMA converged over time, with the

difference between submission dates decreasing significantly over time, from an average of 113.0 weeks in 2009 to 2.4 weeks in 2023 ($p=0.008$) (Figure 3-2).

Figure 3-1 Swimmer plot illustrating regulatory activity timeline for gene and cell-based therapies approved by the FDA and EMA.



Grey area: 95% confidence interval, blue line: regression line.

Figure 3-2 Difference in submission time to FDA and EMA, 2009 to 2022.

The median review duration between submission and approval date was 34.1 weeks (IQR, 29.6, 47.4) for the FDA and 55.8 weeks (IQR, 47.5, 68.1) for EMA. This represented a median difference of 20.9 weeks (IQR, 7.9, 30.4) weeks (p<0.001), with no significant change over time (p=0.27). Overall, the FDA approved applications a median of 23.1 weeks (IQR, 4.5, 49.0) earlier (p=0.15), with the difference in the period between approval dates decreasing significantly over time, from 175.0 weeks in 2010 to 22.8 in 2023 (p=0.003).

For three GCTs, sipuleucel-T, elivaldogene autotemcel, and betibeglogene autotemcel, EMA marketing authorisations were withdrawn within a median of 21 months (range, 4-33) after original approval. Public statements issued by EMA indicated that all three products were withdrawn due to commercial reasons. Two of these withdrawals (elivaldogene autotemcel and betibeglogene autotemcel) occurred during FDA review and prior to FDA approval. Additionally, EMA marketing authorisation for MACI expired in July 2018 with no renewal by the marketing authorisation holder, 60 months after EMA approval and 18 months after the product was

approved by the FDA. All four of these products remained on the U.S. market as of October 2023, and no products were withdrawn in the U.S.

Characteristics of application packages

The 20 application packages included a total of 24 unique primary trials, with 18 (90%) applications including data from a single trial. All applications included one or more multicentre studies, 5 (25%) included at least one randomised trial, 9 (45%) included at least one phase III clinical trial, and 1 (5%) included a blinded trial. There were 15 (75%) applications that relied only on single arm trials, and 12 (60%) that included only trials with surrogate endpoints. Another 6 (30%) applications included trials with clinical endpoints and 2 (10%) with clinical scales. All applications included at least 1 secondary trial, with 6 (35%) applications submitted to the FDA including more than one secondary trial, compared with 8 (47%) submitted to the EMA.

Concordance in clinical evidence reporting

Among the 20 application packages, 17 (85%) included the same primary trials between the FDA and EMA. Among these trials, 7 (41%) were concordant on the sample size, with a median sample size of 90 participants (IQR, 60, 112) in trials submitted to the FDA and 95 (IQR, 75, 140) for those submitted to the EMA ($p = 0.65$) (Table 3-2). Primary endpoints were concordant for 16 (94%) trials. The one exception was the trial supporting the application for valotocogene roxaparvovec, for which the sponsor reported annualised bleeding rate as the primary endpoint to the FDA and factor VIII activity to the EMA. The comparator type was the same for 13 (76%) trials. For the other four trials, the trial report to the FDA did not include a comparator, while the information submitted to the EMA described an external comparator. The efficacy outcome was the same in submissions to the FDA and EMA for 7 (41%) trials. For another 8 (47%) trials, the efficacy outcome reported to the FDA indicated stronger benefits, while for 4 (24%) trials, the efficacy reported to the EMA was superior. Differences in reported efficacy outcomes between the agencies were <10% of the effect size, with the exception of two applications: For axicabtagene ciloleucel's initial indication, the sponsor reported a 20.5% higher overall remission rate to the FDA than to the EMA, even though the data cut-off date reported to the FDA was 6 months earlier than the cut-off date

reported to the EMA. Similarly, for tisagenlecleucel's initial indication, the sponsor reported a 19.6% higher overall remission rate to the FDA than to the EMA, and the data cut-off reported to the FDA was dated 5 months before that reported to EMA.

Table 3-2 Concordance in clinical evidence reporting for primary clinical trials submitted to both the FDA and EMA.

Characteristics of primary trials	Trials with matching values, N (%) (N = 17)
Sample size	7 (41)
Primary endpoint	16 (94)
Comparator type	13 (76)
Efficacy outcome	6 (35)

Across the 4 key trial characteristics, the FDA and EMA were presented with the same evidence from the 17 pivotal trials in only four application packages (talimogene laherparepvec, MACI, sipuleucel-T, and axicabtagene ciloleucel's indication of B-cell lymphoma). Overall, this represented a concordance of 20% (n=4) for evidence reporting for primary clinical trials in the 20 application packages.

For the secondary trials, 9 out of a total 20 (45%) applications submitted the same trials to both the FDA and EMA and for 8 (40%) applications, there was no overlap in submitted secondary trials. There were 6 (30%) applications submitted to the FDA that included more than one secondary trial, compared with 8 (40%) submitted to EMA. When considering these elements from primary and secondary trials, 3 (18%) submission packages were concordant between the FDA and EMA.

Discussion

Our analyses found that drug sponsors tend to submit applications for GCTs earlier to the FDA, however, we see a trend of convergent submission dates to FDA and EMA over time. We found discordances in how the same clinical trials were presented to FDA and EMA upon submission. This discordance largely stems from differences in reported sample size and comparators used in the efficacy analysis, as well as selective inclusion of secondary trials in application packages. In

summary, these results suggest that regulatory agencies are currently presented with different efficacy evidence when deciding on marketing authorisation for GCTs, subject to reporting and timing differences on behalf of the submitting sponsors.

Concerning differences between FDA and EMA submissions, previous studies have largely either focused on submission timing (Lythgoe et al., 2022), or on differences in reporting and assessment (Di Dalla Torre Sanguinetto et al., 2019; Ibrahim & Kadam, 2023; Kashoki et al., 2020). In comparison, we considered both variables in our analysis by considering submission timing and submitted trials and their characteristics which seems to be linked and should be assessed simultaneously (Joppi et al., 2020). The factors that influence the timing of submission might still need to be clarified. Later submission has previously been suggested to strengthen the efficacy evidence presented to EMA, by allowing drug sponsors to include larger sample sizes and more conclusive evidence in their analyses (Lythgoe et al., 2022; Kashoki et al., 2020; Vokinger et al., 2023). Another factor is the different evidence requirements that may already be communicated during advisory meetings before submission, which can be indicative of the anticipated rigor of each agency, pushing sponsors to plan submissions around these requirements. Discrepancies may further arise as sponsors seek full or expedited marketing authorisation by one of the two agencies at some point in time, particularly given the differences between FDA and EMA's expedited pathways (Hwang et al., 2020). Lastly, such discrepancies may also stem from a very narrow or uncertain benefit risk balance of GCT products, leading different analyses and interpretation of results (Cramer et al., 2023). For instance, trials with less robust designs such as non-randomisation and small sample sizes, have been identified as the main driver of regulatory discordance for haemato-oncology products (Rohr et al., 2023).

CoGenT is intended to increase regulatory efficacy by addressing inefficient costs and time of parallel regulatory review by different agencies. To this end, the pilot foresees participation by partner agencies in internal regulatory meetings with sponsors of new GCT applications and shared reviews. These activities aim to incentivise sponsors to invest in rare disease treatments, which are primarily foreseen to benefit from the pilot (Eglovitch, 2024). If projects like the CoGenT pilot are

to harmonise regulatory approval for GCTs across countries, drug sponsors need to align how they present evidence to FDA and EMA. For this purpose, drug sponsors should be made aware of advantages of concurrent submission, such as consolidating resources and expertise in a streamlined process. Further harmonisation of GCT regulation could facilitate knowledge exchange and development of agreed evidence standards for product groups that lack evidence from robust randomised controlled trials (Hatswell et al., 2016) and encourages alignment between the regulatory agencies themselves (Teixeira, Kweder & Saint-Raymond, 2020). In sum, harmonisation could lead to more efficient and rigorous evidence generation and assessment for GCTs. Furthermore, it could help ensure timely reimbursement agreements and patient access (Gonçalves, 2022).

There are several limitations to our study. Our data were limited to publicly available data published by the FDA and EMA at the time of data lock on October 3, 2023. In contrast to the EMA, FDA does not release information on rejected submissions, which prohibited a comparison of all submitted GCT applications. For the primary trial characteristics that we compared, we were unable to determine the underlying reasons for the discrepancies, for example, whether they were related to evolving interpretation of the clinical trial by sponsors or consultations with regulators prior to submission of the application package. Lastly, there may be differences in the product labelling between the FDA and EMA (Vokinger, Glaus & Kesselheim, 2023), which we did not consider, but which may present further opportunity for harmonisation across the agencies.

Conclusion

One of the main aims of harmonisation of regulatory decisions is to accelerate access to innovative therapies, such as GCTs, by reducing the impact of varying regulatory requirements on drug developers. Our analysis indicates submission to the EMA usually followed the submission to FDA and often contained larger efficacy sample sizes and were more often controlled. While we found discordance between the efficacy evidence in GCTs packages submitted to the FDA and EMA, it is hard to ascertain whether this discordance is a product of the varying regulatory environment and whether harmonisation could lead to further concordance among submissions. Building on our

results and further understanding sources of discordance will be empirical for regulators to improve efficiency in drug approval processes. Regulators seem to realise the challenge as evident by the emerging incentives for concurrent submissions and review of evidence.

Bibliography

American Society of Gene and Cell Therapy. 2023. Gene, Cell, & RNA Therapy Landscape Report Q4 2023. Available online via: https://www.asgct.org/global/documents/asgct-citeline-q4-2023-report.aspx?_ga=2.137308658.390641582.1715862232-2015307444.1715774295&_gl=1*1bzyon8*_ga*MjAxNTMwNzQoNC4xNzE1Nzc0Mjk1*_ga_6FB6X4L6XF*MTcxNTg2MjIzNi4zLjEuMTcxNTg2MjI3MC4yNi4wLjA.*_ga_Q37QKR6TCJ*MTcxNTg2MjIzNi4zLjEuMTcxNTg2MjI3MS4wLjAuMA. Last accessed: 06 June 2024.

Barkholt, L., Voltz-Girolt, C., Raine, J., Salmonson, T. & Schüssler-Lenz, M. 2019. Regulatory watch: European regulatory experience with advanced therapy medicinal products. *Nature reviews. Drug discovery, 18*(1): pp. 8–9. DOI: 10.1038/nrd.2018.200

Bravery, C. A., Ball, O. & Robinson, S. 2019. EU market authorisation strategy: lessons from the first 22 ATMP submitted to the EMA. *Cell Gene Therapy Insights, 5*(6): 759–791. DOI: 10.18609/cgti.2019.088

Clement, F. M., Harris, A., Li, J. J., Yong, K., Lee K. M. & Manns, B. J. 2009. Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. *JAMA, 302*(13): 1437–1443. DOI: 10.1001/jama.2009.1409

Cramer, A., Sørup, F. K. H., Christensen, H. R., Petersen, T. S. & Karstoft, K. 2023. Withdrawn accelerated approvals for cancer indications in the USA: what is the marketing authorisation status in the EU? *The Lancet. Oncology, 24*(9): e385-e394. DOI: 10.1016/S1470-2045(23)00357-1

de Wilde, S., Coppens, D. G. M., Hoekman, J., Bruin, M. L. de, Leufkens, H. G. M., Guchelaar, H. J. & Meij, P. 2018. EU decision-making for marketing authorization of advanced therapy medicinal products: a case study. *Nature reviews. Drug discovery today, 23*(7): 1328–1333. DOI: 10.1016/j.drudis.2018.03.008.

Di Dalla Torre Sanguinetto, S., Heinonen, E., Antonov, J. & Bolte, C. 2019. A Comparative Review of Marketing Authorization Decisions in Switzerland, the EU, and the USA. *Therapeutic innovation & regulatory science, 53*(1): 86–94. DOI: 10.1177/2168479018764660

Downing, N. S., Aminawung, J. A., Shah, N. D., Krumholz, H. M. & Ross, J. S. 2014. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA, 311*(4): 368–377. DOI: 10.1001/jama.2013.282034

Eglovitch, J. S. 2024. Top FDA official interested in 'Project Orbis' for cell and gene therapies. Regulatory Focus. https://www.raps.org/News-and-Articles/News-Articles/2023/2/Top-FDA-official-interested-in-Project-Orbis-for-c. Last accessed: 13 June 2024.

Elsallab, M., Bravery, C. A., Kurtz, A. & Abou-El-Enein, M. 2020. Mitigating Deficiencies in Evidence during Regulatory Assessments of Advanced Therapies: A Comparative Study with Other Biologicals. *Molecular therapy. Methods & clinical development, 18*: 269–279. DOI: 10.1016/j.omtm.2020.05.035

European Medicines Agency. 2024. European public assessment reports: background and context. Available at: https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-and-when/european-public-assessment-reports-background-and-context#publications-19138 Last accessed: 06 June 2024.

Food and Drug Administration. 2024a. CY 2023 Report from the Director. Available online via: https://www.fda.gov/vaccines-blood-biologics/cy-2023-report-director. Last accessed: 16 May 2024.

Food and Drug Administration. 2024b. Approved Cellular and Gene Therapy Products. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Last accessed: 06 June 2024.

Gonçalves, E. 2022. Value-based pricing for advanced therapy medicinal products: emerging affordability solutions. *The European journal of health economics: HEPAC : health economics in prevention and care, 23*(2): 155–163. DOI: 10.1007/s10198-021-01276-2

Hatswell, A. J., Baio, G., Berlin, J. A., Irs, A. & Freemantle, N. 2016. Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999-2014. *BMJ open, 6*(6): e011666. DOI: 10.1136/bmjopen-2016-011666

Hwang, T. J., Ross, J. S., Vokinger, K. N. & Kesselheim, A. S. 2020. Association between FDA and EMA expedited approval programs and therapeutic value of new medicines: retrospective cohort study. *BMJ (Clinical research ed.), 371*: m3434. DOI: 10.1136/bmj.m3434

Ibrahim, S. & Kadam, P. 2023. Comparing FDA and EMA Decisions for Market Authorization of Generic Drug Applications covering 2017-2020. White Paper. Office of Generic Drugs, Global Generic Drug Affairs, Food and Drug Administration. https://www.fda.gov/media/156611/download?attachment. Last accessed: 06 June 2024.

Iglesias-Lopez, C., Obach, M., Vallano, A. & Agustí, A. 2021. Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy, 23*(3): 261–274. DOI: 10.1016/j.jcyt.2020.11.008

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2001. Topic E 10. Choice of Control Group in Clinical Trials. https://database.ich.org/sites/default/files/E10_Guideline.pdf. Last accessed: 06 June 2024.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2021. Topic E 8(R1). General Considerations for Clinical Studies. https://database.ich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf. Last accessed: 06 June 2024.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2024a. Mission – Harmonisation for Better Health. Available via: https://www.ich.org/page/mission. Last accessed: 16 May 2024.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2024b. Introductory Guide MedDRA Version 27.0. Available at: https://admin.meddra.org/sites/default/files/guidance/file/intguide_27_0.pdf. Last accessed: 06 June 2024.

Joppi, R., Bertele, V., Vannini, T., Garattini, S. & Banzi, R. 2020. Food and Drug Administration vs European Medicines Agency: Review times and clinical evidence on novel drugs at the time of approval. *British journal of clinical pharmacology, 86*(1): 170–174. DOI: 10.1111/bcp.14130

Kashoki, M., Hanaizi, Z., Yordanova, S., Veselý, R., Bouygues, C., Llinares, J. & Kweder, S. L. 2020. A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014-2016: Concordance, Discordance, and Why. *Clinical pharmacology and therapeutics, 107*(1): 195–202. DOI: 10.1002/cpt.1565

Lythgoe, M. P., Desai, A., Gyawali, B., Savage, P., Krell, J., Warner, J. L. & Khaki, A. R. 2022. Cancer Therapy Approval Timings, Review Speed, and Publication of Pivotal Registration Trials in the US and Europe, 2010-2019. *JAMA network open, 5*(6): e2216183. DOI: 10.1001/jamanetworkopen.2022.16183

Rohr, U. P., Iovino, M., Rudofsky, L., Li, Q., Juritz, S., Gircys, A. et al. 2023. A decade comparison of regulatory decision patterns for oncology products to all other non-oncology products among Swissmedic, European Medicines Agency, and US Food and Drug Administration. *Clinical and translational science, 16*(9): 1569–1581. DOI: 10.1111/cts.13567

Teixeira, T., Kweder, S. L. & Saint-Raymond, A. 2020. Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other?. *Clin. Pharmacol. Ther., 107:* 507-513. DOI: 10.1002/cpt.1617

ten Ham, R. M. T., Hoekman, J., Hövels, A. M., Broekmans, A. W., Leufkens, H. G. M. & Klungel, O. H. 2018. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Molecular therapy. Methods & clinical development, 11*: 121–130. DOI: 10.1016/j.omtm.2018.10.003

Vokinger, K. N., Serra-Burriel, M., Glaus, C. E. G., Rohr, U. P., Hwang, T. J., Di Dalla Torre Sanguinetto, S., Kesselheim, A. S. 2023. Regulatory Review Duration and Differences in Submission Times of Drugs in the United States and Europe, 2011 to 2020. *Annals of internal medicine, 176*(10): 1413–1418. DOI: 10.7326/M23-0623

Vokinger, K. N., Glaus, C. E. G. & Kesselheim, A. S. 2023. Approval and therapeutic value of gene therapies in the US and Europe. *Gene Therapy, 30:* 756–760. DOI: 10.1038/s41434-023-00402-4

Statement of Authorship

Ich erkläre hiermit, dass ich diese Arbeit selbständig verfasst und keine anderen als die angegebenen Quellen benutzt habe. Alle Koautorenschaften sowie alle Stellen, die wörtlich oder sinngemäss aus Quellen entnommen wurden, habe ich als solche gekennzeichnet. Mir ist bekannt, dass andernfalls der Senat gemäss Artikel 36 Absatz 1 Buchstabe o des Gesetzes vom 5. September 1996 über die Universität zum Entzug des aufgrund dieser Arbeit verliehenen Titels berechtigt ist.

Bern, 21.06.2024 Sandra Gillner

Appendices

Appendix – Paper 1

Table 1-i: Interview guide AI providers.

Topic	Question	Probe
Introduction interviewee	1. What is your position in the company?	
	2. What is your educational background?	
	3. What is your role with respect to the technology we are talking about today?	
Introduction technology	4. Could you please start by describing the technology we are about to discuss today?	• What does the software do? • How does it do that?
	5. Which output does the algorithm produce?	
	6. What happens with this output?	• Who is making use of the output? • What are they doing with this output?
Perceived ease-of-use	7. Is specialised training for the adopting organisation necessary to use the product?	• If so, for whom?
Perceived usefulness	8. Consider a healthcare provider deciding to implement the software. Which benefits come with this agreement?	
	9. How are you demonstrating value of the product to interest healthcare providers?	
Costs of adoption	10. Which non-monetary costs of adoption are incurred by adopting hospitals?	
Cooperation	11. *Focusing on your cooperation with healthcare providers:* Could you elaborate on the 'typical customer' for your product?	
Project trajectory	12. Which stakeholders within a hospital are involved when implementing your product?	
	13. From your experience, are there certain phases during the acquisition process that are typically difficult or delayed?	
	14. Could you elaborate on the topic of interoperability of software and data, and on how your company tackles this issue?	
Public policy	15. Would you see an added value of public funding for this type of product?	• Who should be responsible for funding such technologies?
	16. Which role do you see for policy makers regarding the adoption of this type of product?	
Learnings	17. Which lessons did you take away from your experience with making the product accessible?	
	18. Which implications do these lessons have as you are further developing the product and your business model?	

Table 1-ii: Interview guide adopting organisations.

Topic	Question	Probe
Introduction interviewee	1. What is your position in the organisation?	
	2. What is your educational background?	
	3. What is your role with respect to the technology we are talking about today?	
Acquisition trigger	4. What triggered the process of acquiring this product?	• Did you identify a specific need or interest? • Who approached whom?
Expectations	5. Could you elaborate on your expectations of adopting this new technology?	
Identification of decision-making units	6. Who were the key decision makers involved in deciding about the acquisition of the software?	• You just mentioned *X*, *Y*, and *Z*. Which roles do these people take on in the hospital?
Bottlenecks	7. Were there certain phases during the acquisition process that were particularly difficult or delayed?	
Outcome	8. Did the adoption of the algorithm deliver additional income for your organisation?	
	9. *If so*: Did the additional income occurred change or stimulate the funding of the technology?	
	10. Were there any unintended consequences of adopting the product?	
	11. (*The algorithm has now been implemented and has been in use at your hospital for some time.*) Have your expectations towards the algorithm been fulfilled?	
Perceived usefulness	12. Which added value does the product represent to you?	
Public policy	13. Would you see an added value of public funding for this type of product?	• Who should be responsible for funding such technologies?
	14. Do you consider a role for policy in the context of technology adoption for diagnostic software using AI?	
Sense-making of technological innovation	15. How would you describe your hospital's culture towards innovation?	• Is management embracing innovation or shying away from it?
	16. How important is it for your organisation to be investing in the newest technologies?	• Why (not)?

Appendix – Paper 2

Table 3-i: Interview guide participants at t1.

Introduction	Question	Probe
We would like to speak to you about the collaborative [QIC name censored] and your own initiative within this collaborative. This program was separated into two phases: First, the online-based learning phase, second, the implementation phase.	1. Let us start with a rating: On a scale from zero to ten, where zero indicates not helpful at all and ten indicates very helpful: As how helpful would you rate the learning phase for the subsequent implementation of your initiative in your own organisation?	• What has been particularly helpful to you during the learning phase? • You indicated a *[rating]*. What would have to be improved or changed for you to rate the helpfulness of the learning phase a ten?
Please try to recall now the other participants in the collaborative – as you know, you were a group with diverse organisational and professional backgrounds.	2. As how helpful did you experience this professional diversity among the group of participants?	• Do you have a concrete example for a situation in which this diversity was particularly helpful/not helpful?
	3. Did this diversity in the group ever present a challenge to your learning or implementation endeavour?	• Do you have a concrete example for a situation in which this diversity was challenging to you?
Please think back to the implementation of your own initiative in your organisation.	4. What were necessary conditions for the implementation of your initiative?	• You already indicated several factors on the organisational level. Can you think of any factors related to the collaborative? *(And vice versa).*
	5. What were helpful, but not necessary factors for the implementation of your initiative?	• You already indicated several factors on the organisational level. Can you think of any factors related to the collaborative? *(And vice versa).*
	6. You have mentioned factors *X, Y*, and *Z*. Please rank these factors by importance.	• Why did you rank these factors as you did?
	7. Which challenges did you experience when implementing your project?	

	8. What did you do to overcome these challenges?	
	9. If you failed to overcome some of these challenges, what would you have needed in order to overcome them?	
Please try to remember when you first started this project in your organisation.	10. How would you rate your initial motivation to implement this initiative on a scale from zero to ten?	• Why?
	11. How would you rate your current motivation to implement this initiative on a scale from zero to ten?	• Why?
	12. How would you rate your current success of implementing this initiative on a scale from zero to ten?	• Why?
We have nearly reached the end of the interview.	13. Do you have any advice for the organisers of this collaborative?	• Please think back to your own experience in this collaborative. What could have been improved?
	14. Do you have any advice for future participants of such collaboratives?	
	15. Is there anything else you would like to add?	

Table 2-ii: Interview guide participants at t2.

Introduction	**Question**	**Probe**
We will shortly speak about your experiences during the past ten months since we last spoke. First, I would like to talk with you about the current status of your initiative.	1. How would you describe the current status of your initiative in your organisation?	• Could you compare the current status of the initiative with the status in *T1*?
		• To what extent is the initiative **known** among employees? • To what extent is the initiative **used** by employees? Are there any differences among the employees? If so, which ones?
Let us talk about your experiences within the past ten months.	2. How would you describe the development of your initiative within the past ten months?	• Which phases were particularly challenging to you? • Which phases did you perceive as particularly successful?
Let us talk in more detail about how implementation of this initiative changed your work in your organisation.	3. How did implementing your initiative change your relationships to your colleagues?	• Do you have concrete examples which illustrate these changes?
	4. How important was exchanging with other colleagues in your organisation for the implementation of your initiative?	• Why?
	5. Could you give a concrete example of a situation when this exchange was particularly important for implementing your initiative?	• How easy or difficult was it for you to navigate these situations?
Now I would like to talk about the sustainability of your initiative with you. For this purpose, let us consider sustainability as the degree to which your initiative is active, and the necessary resources are available within your organisation over a longer period of time.	6. As how sustainable would you rate your initiative on a scale from zero to ten? A zero would indicate that the initiative does not exist anymore and a ten would indicate that the initiative is fully active, and resources are available in your organisation over a longer period of time.	• Why did you rate sustainability a *[rating]*?

	7. How did you try to ensure that your initiative is sustainable?	• Which other factors helped to sustain your initiative?
	8. What would you have needed to further ensure the sustainability of your initiative?	
During our last conversation in [name month t1], *I asked you to rate the success of your initiative on a scale from zero to ten.* *Ten months ago, you ranked the initiative's success a* [old rating].	9. If you think back to our conversation thus far, how would you currently rate the success of your initiative on a scale from zero to ten?	
We have nearly reached the end of the interview.	10. Are you still in contact to other participants from the collaborative?	
	11. Is there anything else you would like to add?	

TABLE 2-iii: Deductive coding scheme stages of implementation (deductive; adapted from Fixsen et al. 2005).

Stage	Description of activities	Needs of the QI initiative	Corresponding data segment (examples)
Exploration	• Acquiring information and exploring options. • Assessing the potential match between a planned intervention and organisational needs. • Preparing organisation for mobilizing support.	• Information about staff needs and organisational context. • Knowledge on quality improvement strategies, particularly evidence-informed interventions, to inspire and inform conceptualisation.	"The difficulty for me was actually to think about what to do – in other words, what the project is [about], [...] and to understand what is actually important for us right now. And yes, this took me a very, very long time and it basically only became clear towards the end [of the QIC]." (P1 t1)
Installation	• Consuming resources in active preparation for creating change. • Putting structural supports in place.	• Funding streams. • Human resource strategies, in case of staffing changes. • Accountability structures.	"What I would need is simply an openness, for people to say: Okay, we're going to get this program up and running – this is not about me personally, but about occupational health. I think that the IT people need to be informed at an early stage of planning to make this possible. To be honest, I don't know whether the app will end up being fit for purpose." (P2 t1)
Initial implementation	• Generating usage of the project via the first "consumers". • Testing activities and structures, first feedback is received.	• Overcoming mistrust of new practices and fear of change and inertia. • Feedback of first users to improve the project and adjust it to organisation-wide scale up.	"So, these are [currently] two small pilot projects, one in a ward and one in a nursing home. That means we may not even have covered one tenth of our staff. That means something really has to happen in the future." (P5 t2)
Full operation	• Serving the "full client load". • Realizing project benefits. • Routinizing new activities.	• Stable resource access. • Broad feedback for sustained improvement and acceptance across organisation beyond initial user-base.	"Communication with staff was very important. And it was also nice to see, once again, that everyone deals with things very openly and honestly and that we were really able to inspire the care home management and nursing staff. [...] So the employees have become more aware, and many are now taking occupational health more seriously." (P7 t2)

TABLE 2-iv: Overview of participating organisations and individual QI interventions within QIC.

Interviewee No.	Organisation (type)	Organisational role of the QI project leader	QI intervention	Implementation stage reached by t_2
1	Nursing home	Human resources	Steering committee for occupational health management	Installation
2	Hospital	Occupational Health Management	Health and well-being app for hospital staff	Initial implementation
3	Nursing home	Nursing care management	Mental health program for nursing staff	Full operation
4	Hospital	Executive management	Corporate health and fitness program	Full operation
5	Hospital	Executive management	Steering committee for occupational health management	Full operation
6	Hospital	Human resources	Corporate health and fitness program	Full operation
7	Nursing home	Human resources	Regulated recovery periods for nursing staff	Initial implementation
8	Nursing home	Executive management	Regulated recovery periods for nursing staff	Installation
9	Nursing home	Nursing care management	Steering committee for occupational health management	Exploration
10	Nursing home	Executive management	Steering committee for occupational health management	Exploration

TABLE 2-v: Social network effects during progression across QI implementation stages.

Stage transition	Egocentric network structure	Social network effect	Mode of action	Corresponding data segment (example)
Exploration to installation	Betweenness centrality	**Facilitating** implementation through better information flow between organisational units	Eliciting needs from remote staff members	"The most important factor in starting the project was that the health advisory board comes from such diverse subdivisions that hopefully we can represent the entire workforce." (*P2 t1*)
			Embedding the new QI project in existing organisational structures	"One difficulty was that there were already somehow outdated but established structures that first had to be broken down. And not to offend anyone, as though to say: 'I'm going to come and redo this' and go away again but rather to include those who have already been involved with the topic at some point, or who are still involved in the structures, instead of pushing them away." (*P4 t1*)
	Density	**Hindering** implementation by reinforcing information redundancy and old beliefs	Joint approval or rejection of new implementation plans	"So here in this organisation everyone focused on integration interviews, after a long sick leave, but [occupational health management] isn't just that. I must admit that we have not yet implemented anything here. We have met two or three times and to be honest, not much has come of it. I even asked how important this project is to the participants who are in this steering group (*deep exhale*). I find it difficult." (*P9 t1*)
Installation to initial implementation	Density	**Facilitating** implementation by fostering trust and shared sense-making	Common goal setting	"Generally, I would say that [the team] is a little bit more open in the sense that they're communicating and they're also realizing that they're being heard [...]. When we had team meetings, we often got asked: Where are we right now and when are we going to start properly?" (*P8 t_2*)
			Garnering project support	"Of course, [you need] your own team or the internal structure of each individual's team, because if you don't get any support there you can't implement everything on your own. You can be skilled; you can have aspirations and wishes. But if you don't have the support of the management and your own team, you obviously can't implement all the projects you have in mind." (*P7 t1*)

	Degree centrality	**Facilitating** implementation through network influence	Allocating time resources	"[An absolutely necessary condition was] that we got the support and freedom to do it, and that we can even work on it during the working hours." (*P6 t1*)
Initial implementation to full operation	Betweenness centrality	**Facilitating** implementation through better information flow between organisational units	Expanding the initial user base to the full intended scope	"After we checked the numbers, we saw that basically very few staff from the nursing homes had signed up. We had had a concerted effort here at the hospital, there were employees from (*anon. sports provider*), answering questions. So I took the initiative and went to the nursing homes and held a small information event there. I also got to know the management and I was able to talk to some of the staff so that they can connect a face with occupational health management from now on." (*P2 t_2*)
	Density	**Facilitating** implementation through group thinking and collective goal setting	Strengthen ongoing cooperation	"I have already had a few quality circles on the subject in one facility and the home management, nursing service management, and all participants in the quality circle were totally enthusiastic and really worked very constructively. [...] Where we are at the moment, I think it is a success. If only because the employees and the managers really think it's great and already have great ideas and really want to continue working on this project." (*P7 t_2*)

Appendix – Paper 3

Table 3-i: Overview of GCT marketing authorization applications matched by indication.

International non-proprietary name	Commercial name	Product type	Indication	Disease area (MedDRA)	Orphan designation date EMA	Orphan designation date FDA	PRIME date	Breakthrough date	Submission date EMA	Marketing authorization date EMA	Withdrawal date EMA	Submission date FDA	Marketing authorization date FDA
Axicabtagene ciloleucel	Yescarta	Gene therapy	DLBL†	Neoplasms	2014-12-16	2014-03-27	2017-07-29	2015-12-03	2017-07-29	2018-08-23	n/a	2017-03-31	2017-10-18
			B-cell lymphoma	Neoplasms	2014-12-16	2014-03-27	n/a	2015-12-03	2021-11-05	2022-10-17	n/a	2021-09-30	2022-04-01
			Follicular lymphoma	Neoplasms	2015-11-11	2014-03-27	n/a	2015-12-03	2021-07-23	2022-06-28	n/a	2020-09-03	2021-03-05
Betibeglogene autotemcel	Zynteglo	Gene therapy	Thalassaemia beta	Blood and lymphatic system disorders	2013-01-23	2013-03-18	2016-09-15	2015-01-29	2018-08-21	2019-05-29	2022-03-24	2021-09-20	2022-08-17
Brexucabtagene autoleucel	Tecartus	Gene therapy	Mantle cell lymphoma†	Neoplasms	2019-11-13	2016-04-28	2018-06-01	2018-06-15	2020-01-09	2020-12-14	n/a	2019-12-11	2020-07-24
			ALL	Neoplasms	2020-10-19	2016-04-20	n/a	2017-12-20	2021-06-01	2022-09-06	n/a	2021-03-31	2021-10-01
Ciltacabtagene autoleucel	Carvykti	Gene therapy	Plasma cell myeloma	Neoplasms	2020-02-28	2019-02-01	2019-03-28	2019-12-06	2021-04-29	2022-05-25	n/a	2021-03-31	2022-02-28
Elivaldogene autotemcel	Skysona	Gene therapy	Adrenoleukodystrophy	Metabolism and nutrition disorders	2012-06-06	2012-04-19	2018-07-26	2018-05-21	2020-09-10	2021-07-16	2021-11-18	2021-10-18	2022-09-16
Etranacogene dezaparvovec	Hemgenix	Gene therapy	Factor IX deficiency	Blood and lymphatic system disorders	2018-03-21	2019-04-17	2017-04-21	2017-01-25	2022-03-07	2023-05-20	n/a	2022-03-24	2022-11-22
Idecabtagene vicleucel	Abecma	Gene therapy	Plasma cell myeloma	Neoplasms	2017-04-20	2016-05-11	2017-11-10	2017-09-19	2020-04-30	2021-08-18	n/a	2020-07-27	2021-03-26
Lisocabtagene maraleucel	Breyanzi	Gene therapy	DLBL	Neoplasms	2017-07-17	2016-04-27	2016-12-15	2016-12-15	2020-06-29	2022-04-04	n/a	2019-12-18	2021-02-05
MACI	MACI	Cell-bsed therapy	Chondropathy	Musculoskeletal and connective tissue disorders	n/a	n/a	n/a	n/a	2011-09-01	2013-06-27	2018-07-01	2016-01-04	2017-12-13
Onasemnogene abeparvovec	Zolgensma	Gene therapy	Spinal muscular atrophy	Musculoskeletal and connective tissue disorders	2015-06-19	2014-09-30	2017-01-26	2016-07-15	2018-10-09	2020-05-18	n/a	2018-10-01	2019-05-24
Sipuleucel-T	Provenge	Cell-based therapy	Prostate cancer	Neoplasms	n/a	n/a	n/a	n/a	2011-12-30	2013-09-06	2015-05-06	2009-10-30	2010-04-29
Talimogene laherparepvec	Imlygic	Gene therapy	Malignant melanoma	Neoplasms	n/a	2011-03-14	n/a	n/a	2014-08-28	2015-12-16	n/a	2014-07-28	2015-10-27
Tisagenlecleucel	Kymriah	Gene therapy	ALL†	Neoplasms	2014-04-29	2014-01-31	2016-06-23	2016-02-29	2017-11-02	2018-08-23	n/a	2017-02-02	2017-08-30
			DLBL	Neoplasms	2016-10-14	2017-08-29	2016-06-23	2017-04-12	2017-11-02	2018-08-23	n/a	2017-10-27	2018-05-01
			Follicular lymphoma	Neoplasms	2021-07-19	2020-09-16	n/a	n/a	2021-08-31	2022-04-29	n/a	2021-08-27	2022-05-27
Valoctocogene roxaparvovec	Roctavian	Gene therapy	Factor VIII deficiency	Blood and lymphatic system disorders	2016-03-21	2016-02-29	2017-01-27	2017-10-24	2021-06-25	2022-08-24	n/a	2022-09-29	2023-06-30
Voretigene neparvovec	Luxturna	Gene therapy	Retinal dystrophy	Eye disorders	2012-04-02	2016-11-29	n/a	2014-09-24	2017-07-29	2018-11-22	n/a	2017-05-16	2017-12-19

MACI = Matrix applied characterised autologous cultured chondrocytes; DLBL = Diffuse large B-cell lymphoma; ALL = Acute lymphocytic leukaemia; † Initial indications, if multiple marketing authorizations were matched for one product. Date format: YYYY-MM-DD.

Table 3-ii: Overview of reported trial characteristics.

INN	NCT	Trial phase	Multicentre	No. of trial arms	Randomization	Blinding	Sample size EMA	Sample size FDA	Primary endpoint EMA	Primary endpoint FDA	Comparator type EMA	Comparator type FDA	Efficacy outcome EMA	Efficacy outcome FDA
Axicabtagene ciloleucel	NCT02348216	II	Yes	1	No	No	111	101	ORR	ORR	external	none	66 %	83%
Axicabtagene ciloleucel	NCT03391466	III	Yes	2	Yes	No	359	359	EFS	EFS	active	active	0.398	0.398
Axicabtagene ciloleucel	NCT03105336	II	Yes	1	No	No	75	81	ORR	ORR	none	none	91%	91%
Betibeglogene autotemcel	NCT02906202	III	Yes	1	No	No	5	23	TI	TI	external	external	80%	91%
Brexucabtagene autoleucel	NCT02601313	II	Yes	1	No	No	60	60	ORR	ORR	none	none	85%	65%
Brexucabtagene autoleucel	NCT02614066	I/II	Yes	1	No	No	78	54	OCR	OCR	external	none	73.10%	87%
Ciltacabtagene autoleucel	NCT03548207	I/II	Yes	1	No	No	97	97	ORR	ORR	external	none	97.90%	97.90%
Elivaldogene autotemcel	NCT01896102	II/III	Yes	1	No	No	17	26	Month 24 MFD-free survival	Month 24 MFD-free survival	external	external	88%	88%
Etranacogene dezaparvovec	NCT03569891	III	Yes	1	No	No	54	54	Annualized bleeding rate (ABR)	Annualized bleeding rate (ABR)	external	external	0.36	0.46
Idecabtagene vicleucel	NCT02773030	II	Yes	1	No	No	140	100	ORR	ORR	external	none	67.10%	72%
Lisocabtagene maraleucel	NCT02631044	I	Yes	1	No	No	216	192	ORR	ORR	none	none	72.70%	73.40%
MACI	NCT00719576	III	Yes	2	Yes	No	144	144	- KOOS pain - KOOS function	- KOOS pain - KOOS function	active	active	- KOOS pain = 11.8 - KOOS function = 11.4	- KOOS pain = 11.8 - KOOS function = 11.4
Onasemnogene abeparvovec	NCT03306277	III	Yes	1	No	No	22	21	- Survival at 14 months of age - Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age	- Survival at 14 months of age - Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age	external	external	- survival = 90.9% - sitting = 59%	- survival = 67% - sitting = 47%
Sipuleucel-T	NCT00065442	III	Yes	2	Yes	Yes	512	512	OS	OS	placebo	placebo	0.775	0.775
Talimogene laherparepvec	NCT00769704	III	Yes	2	Yes	No	436	436	Durable response rate (DRR)	Durable response rate (DRR)	active	active	16.30%	16.30%
Tisagenlecleucel	NCT02435849	II	Yes	1	No	No	92	63	Overall remission rate	Overall remission rate	none	none	66.30%	82.50%
Tisagenlecleucel	NCT02445248	II	Yes	1	No	No	95	68	ORR	ORR	none	none	51.60%	50%
Tisagenlecleucel	NCT03568461	II	Yes	1	No	No	94	90	Complete response rate (CRR)	Complete response rate (CRR)	none	none	69.10%	67.80%
Valoctocogene roxaparvovec	NCT03370913	III	Yes	1	No	No	134	112	FVIII activity	Annual bleeding rate (ABR)	external	external	23.92 IU/dL	-2.8 bleeds/year
Voretigene neparvovec	NCT00999609	III	Yes	2	Yes	No	29	31	Change in multi-luminance mobility test score (MLMT)	Change in multi-luminance mobility test score (MLMT)	no treatment	no treatment	1.6	1.8

INN = International non-proprietary name. MACI = Matrix applied characterised autologous cultured chondrocytes; OS = Overall survival; ORR = Overall response rate; TI = Transfusion independence; EFS = Event-free survival; OCR = Overall complete remission; KOOS = Knee Injury and Osteoarthritis Outcome Score.

Table 3-iii: Average Difference of submission dates between FDA and EMA per year (absolute value).

Year of first submission to either FDA or EMA	Average difference in submission dates (weeks)
2009	113
2011	227
2014	4.43
2017	16.9
2018	81
2019	15.9
2020	38.8
2021	16.9
2022	2.43

Table 3-iv: Average Difference of approval dates between FDA and EMA per year (absolute value).

Year of first approval by either FDA or EMA	Average difference in approval dates (weeks)
2010	175
2013	233
2015	7.14
2017	47.9
2018	16.3
2019	110
2020	20.4
2021	48.5
2022	22.8

Table 3v: Summary statistics for review timelines.

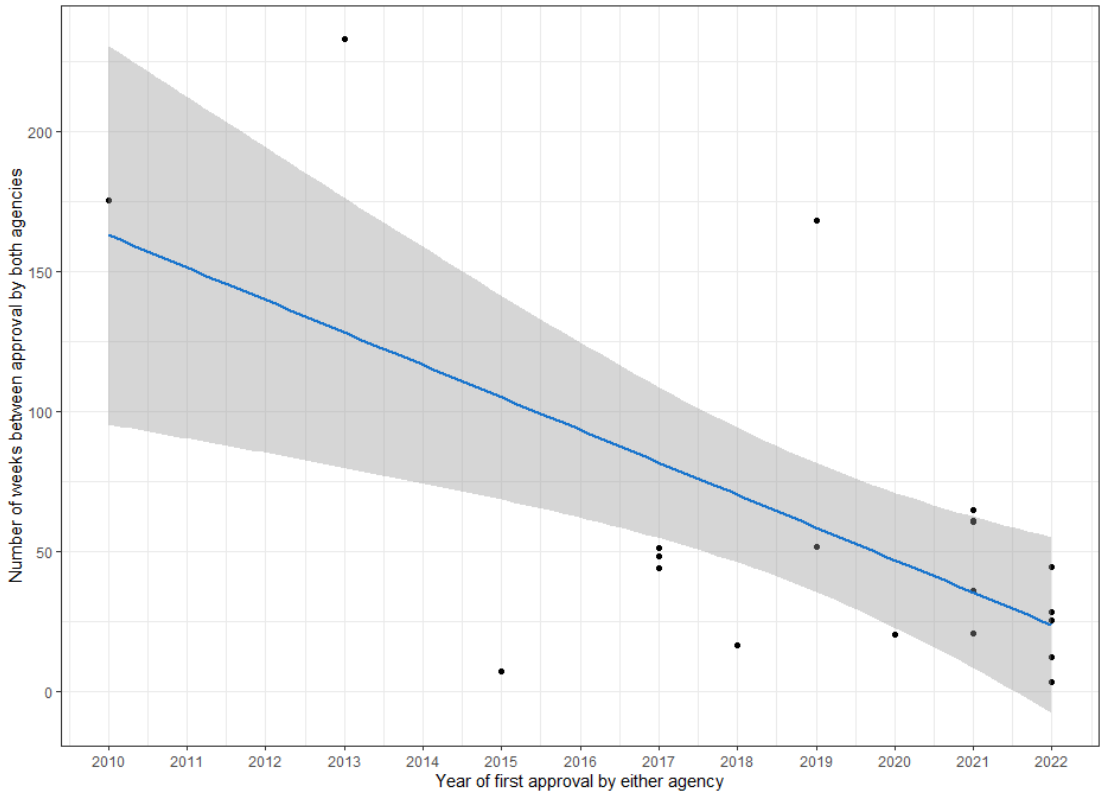
Testing variable	Median	IQR	p-value	n
Difference in submission dates (FDA-EMA [weeks])	-4.143	-12.214, 4.964	0.5135	20
Difference in approval dates (FDA-EMA [weeks])	-23.143	-49.00, -4.536	0.1536	20
Difference in review duration (weeks)	20.857	7.893, 30.357	0.0002098	20

P-value indicates significance determined via Wilcoxon signed-rank test for matched samples. *n* reports number of paired observations.

Table 3-vi: Standardised regression estimates for changes in review timelines.

Relationship	Standardised estimate	SE	p-value
Year of first submission → Submission date difference	-10.161**	3.406	0.00797
Year of first approval → Approval date difference	-11.596**	3.362	0.00286
Year of first submission → Review duration difference	-1.209	1.058	0.268

Figure 3-i: Difference in approval time to FDA and EMA, 2010 to 2022.



Grey area: 95% confidence interval, blue: regression line.