IMPLEMENTATION SCIENCE
Fast track to clinical innovation
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IMPLEMENTATION SCIENCE IN HEALTHCARE TECHNOLOGY INTEGRATION

Foreword

As we celebrate the fifth anniversary of the Eindhoven Medtech Innovation Center (e/MTIC), we reflect on our journey. The mission of e/MTIC is not merely to foster the development of ideas generated by doctors and nurses on the hospital floor. In collaboration with engineers from the technical university, we strive to transform these ideas into effective products and, with the aid of the business sector, bring them back to the workplace to benefit patients directly. Our motto, “the fast track to clinical innovation,” is a testament to our commitment. However, we recognize that it typically takes an average of 17 years for an evidence-based innovation to be implemented in practice. Implementation science is the field that addresses the challenges of the dilemmas inherent in this process. This book aims to shed light on these complexities by giving voice to key figures involved in the journey from ideation to solution and product creation. We have chosen an example from clinical practice that encapsulates the entire trajectory from idea to product development and implementation in clinical settings. Specifically, this involves the development of a new monitoring system for mother and child during pregnancy and childbirth, but can be replaced by any other idea. Our journey in this case, as in many others, spanned 20 years, aligning with the typical 17-year timeframe for clinical implementation.

During the third Lambrey conference, we reflected with researchers from the Fundamental Perinatology Research Group, along with representatives from the hospital, technical university, business sector, and health insurers, on the journey we have made. We hope this book not only imparts knowledge but also sparks inspiration, motivating readers to contribute positively to the healthcare sector. Embark on this enlightening journey with us and discover the intricate dance of implementation science.

Professor Guid Oei, MD PhD
Maxima Medical Center
Eindhoven University of Technology
Eindhoven MedTech Innovation Center
Implementation science, often termed implementation research, stands at the nexus of theory and practice. This multidisciplinary arena emphasizes the systematic exploration of strategies that facilitate the seamless integration of evidence-based interventions, practices, or innovations into real-world settings, particularly in healthcare environments like hospitals.

The primary objective is to narrow the chasm between empirical research and pragmatic application. This endeavor necessitates the scrutiny of a myriad of variables, ranging from the dynamics among healthcare professionals, the interplay of institutional policies and the patients’ perspectives to the overarching infrastructure of the healthcare ecosystem. The ultimate ambition is to craft strategies that accentuate the advantages of new technologies while minimizing potential impediments.

Key aspects of implementation science when rolling out new technologies in hospitals include:

1. Evidence Evaluation: A deep dive into the existing scientific literature to gauge the efficacy, safety, and applicability of the technology in question, identifying any gaps or lacunae that need to be addressed.

2. Barrier & Facilitator Identification: Recognizing potential hindrances and accelerators for implementation. These variables can range from technical details and the way in which an organization thinks and acts to the bigger picture of how the healthcare system works.

3. Strategizing for Implementation: Designing and validating strategies that bolster the adoption and ongoing utilization of new technologies. This often involves training modules, policy amendments, workflow tweaks, innovative study design, and enhanced communication mechanisms.

4. Outcome Assessment: Measuring the real-world impact of implementation strategies, gauging metrics such as adoption rate, fidelity to original design, and long-term sustainability.

5. Scale-up & Dissemination: Following the identification of efficacious strategies, the focus shifts to amplifying the technology’s reach across diverse healthcare settings, buttressed by well-designed dissemination blueprints and guidelines.

By embracing the methodologies of implementation science, healthcare institutions stand poised to augment patient outcomes through the adept introduction of new technological paradigms.

Real-world Case Studies & Insights
Dr. Guid Oei’s own PhD research project in the 1990s, which focused on the effectiveness of the postcoital test introduced by Dr. Sims in the nineteenth century, exemplifies the challenges associated with implementation. Under the guidance of Prof. Marc Keirse, a vanguard in the evidence-based medicine domain, Oei embarked on a novel randomization approach. Though the test was found redundant and was swiftly phased out in the US, the Netherlands witnessed an 18-year lag in its discontinuation - a testament to the intricacies of de-implementation. Historically, the cholera epidemic in 1844 sheds light on implementation disparities. Dr. Eugene Sue’s revelations in Paris linking cholera to hygiene weren’t enough to prevent an outbreak in the small village of Lambrey in the Haute Saône more than a decade later, leading to hundreds of unnecessary deaths.

It seems that local conditions where the implementation takes place play a crucial role in the speed of implementation. The delay in the Netherlands in discontinuing the postcoital test as part of fertility examinations can be
In this context, Laura Damschroder’s ‘Consolidated Framework for Implementation Research’ (CFIR) stands out as a beacon. The CFIR meticulously demarcates potential factors under five broad domains that can influence implementation:

- Intervention Characteristics
- Outer Setting
- Inner Setting
- Characteristics of Individuals
- Process

A case in point is Rebecca Hamm’s foray into obstetrics. The introduction of an ‘obstetric haemorrhage bundle’ bore contrasting results in Pennsylvania and California. The defining difference? California’s recourse to the CFIR framework. Apart from the CFIR, other frameworks for implementation have been developed and validated as well. It probably doesn’t matter much which framework you use; what’s more important is to have a framework in the first place.

Key Takeaways:
1. The indispensability of a structured framework.
2. The imperative of stakeholder engagement.
3. The weightage of qualitative research.
4. The importance of documentation and knowledge dissemination.
5. Gleaning insights from real-world scenarios.

In the world of medicine, technology is assuming an increasingly significant role. The collaboration between technician and clinician in this process is essential. This collaboration can be challenging, but when optimized it will give new opportunities. The different aspects within this collaboration will be further illustrated in order to harmonize medicine and engineering in scientific research and clinical implementation.
Frequently mentioned possible barriers in the collaboration between technicians and clinicians are different communication styles (e.g., jargon), various visions and interests, different responsibilities and diverse types of knowledge. When looking at technical innovations, technicians tend to develop complex solutions whereas clinicians desire a more practical solution. Due to this knowledge gap, technicians are often not involved in the beginning of a research project. Additionally, clinicians sometimes have a conservative mindset regarding (technical) innovations in clinical care. On the other hand, technicians sometimes come up with solutions that lack clinical insight.

Abovementioned barriers are noticeable in all research stages. The typical pathway of clinical research for a clinician consists of the following components: 1) idea, 2) design, 3) execution, 4) data processing and 5) reporting (Figure 1). The technician’s entry point into research typically comes later, as technicians often conduct their research on clinical data. This often results in conflicts during research due to a mismatch in expectations and responsibilities in data collection. For example, technicians are often unaware of the labour intensity and clinical implications of certain procedures. In the most optimal setting, technicians are involved in the first and second stage of a clinical study.

The difference between technical and clinical research is further illuminated by the possibility of adapting or extending research with new ideas. While technicians can easily design new research questions using the collected data, clinicians often need to set up completely new research due to clinical research regulations.

Our recommendations for the advancement of clinical research implementation can be summarized as follows (Figure 2):

- Communication in each stage of the research project is essential.
- Technicians and clinicians should learn to speak the same language.
- Regular (informal) meetings could contribute to overcoming the knowledge differences between clinicians and technicians.
- Regular (informal) meetings could result in new research ideas.

The MDR is a regulation, directly applicable in all EU countries. It governs patient safety and compliance with it leads to a CE mark, which is valid throughout Europe. This MDR also applies to clinical studies. The former directive was no longer adequate, a fact that became evident through various scandals, such as the breast implant incident.

Changes in the MDR compared to the previous situation include: more clinical evidence is required, as is increased transparency; there’s a greater emphasis on post-surveillance research and a shift in classifications, with many products moving to higher classes. This means there’s a quicker need for a notified body. A notified body evaluates the evidence of whether a medical device is safe and meets the CE mark standards. They have the authority to award the CE mark. Every device now carries a Unique Device Identification (UDI) code. Additionally, the EU has set up Eudamed, the European database in which all medical devices are listed and where all ongoing studies are tracked.

What do you need in the regulatory domain to implement your product in the clinic? The primary requirement is the Medical Device Regulation (MDR).

In this session, we will study some of the required technical documents and the logic behind them. Additionally, we will also delve into Artificial Intelligence (AI) ethics, which will soon be legislated by the EU.
market. It’s not only the manufacturer that is subject to the MDR, but also the supply chain partners. The implications of this can be extensive, to the point where certain MDs might no longer be available for patient care. Apart from the MDR, there are other laws, standards, and guidelines documents that one may encounter, such as the ICH GCP (Good Clinical Practice), the Dutch law on medical scientific research.

EU AI Legislation is currently being developed and is aimed at ensuring fundamental rights and safety. Additionally, it is part of a digital framework including laws on the AI liability framework, safety regulations, the Cybersecurity Act, etc.

For AI, a risk classification has been established with four levels. Within this framework, risk is firstly defined as high risk if it is a medical device. Secondly, an AI system is considered to be high risk if it is a safety component of products such as medical devices.

This doesn’t necessarily mean that certain activities or applications are prohibited, but that there are heightened requirements in terms of transparency. Ten standards are going to be established for AI systems:

HIGH-RISK SYSTEM STANDARDS
1. Risk management systems
2. Governance and quality of datasets used to build AI systems
3. Record keeping through logging capabilities by AI systems
4. Transparency and information provisions to the users
5. Human oversight of AI systems
6. Accuracy specifications for AI systems
7. Robustness specifications for AI systems
8. Cybersecurity specifications for AI systems
9. Quality management system for providers of AI systems, including postmarket monitoring process
10. Conformity assessment for AI systems

For example, No. 1 addresses the role of the human being, e.g., the one who bears responsibility. No. 5 pertains to data collection, emphasizing the importance of avoiding bias, but also regarding discrimination and tackling the complexity of acting on AI’s predictions.

There is also an ethical standard comprising seven ethical principles, often used in research. It adopts a lifecycle approach, meaning that these items must be continually reviewed and addressed.

ETHICAL STANDARDS IN AI
THE ALTAI PRINCIPLES DISCUSSION
1. Human agency and oversight
2. Technical robustness and safety
3. Privacy and data governance
4. Transparency
5. Diversity, non-discrimination, and fairness
6. Environmental and societal well-being
7. Accountability

Probably also: human rights assessment, democratic values and rule of law

For example: No. 1 addresses the role of the human being, e.g., the one who bears responsibility. No. 5 pertains to data collection, emphasizing the importance of avoiding bias, but also regarding discrimination and tackling the complexity of acting on AI’s predictions.

While these principles are set, implementing them requires collaboration from all disciplines to make the right decisions, not just ethicists, for example.

Implementation Science: A Beacon of Hope for Low/Middle Income Countries’ Healthcare?

Anne van Tetering MD, Ella de Vries MD and Kirsten Thijssen MD, PhD students of Máxima Medical Center and Eindhoven University of Technology

Low/middle income countries with concurrent low health status of the population stand to benefit more from implementation science in healthcare than high-income countries, given the triad of high need, high potential, and low existing capacity. Nonetheless, studies about implementation science have shown that a technology (or a training course, a protocol, etc.) which works in one setting under certain conditions may not be appropriate in other circumstances. One important aspect to consider is a difference in cultures between the place where a technology was developed and where the technology is intended to be implemented. To understand differences in cultures between countries, the theory of the Culture Map by Meyer can be used. In this theory, national cultures have been mapped on eight scales (Fig 1.). We will highlight three of these scales and give examples of how these differences can lead to challenges, drawing from past experiences in the Netherlands, China and Uganda.

Communicating
Meyer differentiates low-context communication from high-context communication. In countries with low-context communication, messages are expressed and understood at face value. Good communication means it is precise, simple and clear, and repetition is appreciated. In contrast, in countries with high-context communication, messages are spoken and read between the lines. They are implied but not plainly expressed and good communication is sophisticated, nuanced, and layered. As a result, people from low-context cultures, a country where low-context communication is appreciated, will often misunderstand people from Uganda or China, countries with high-context communication. For example, when attempting to get ethical clearance for research in Uganda, it was very unclear to the Dutch people on our team what steps had to be taken, even after asking repeatedly. Therefore, walking into a room and having to present our whole study to the board of the medical ethical committee without previous notice came as a great surprise to the Dutch. It is highly likely the Ugandan counterparts had implied this, but the message was missed by the Dutch. Another example is the tendency of people in low-context communication societies to send emails after a meeting, summarizing the discussion, recording agreements and highlighting tasks that have been assigned. In high-context communication styles, this can be seen as offensive and distrusting. It is also interesting to note that counter-intuitively, the highest chance of miscommunication lies between one high-context person and another high-context person from another culture, as the messages that are conveyed between the lines are completely different.

Evaluating
In Meyer’s theory, countries can range from a direct negative feedback style to an indirect one. The direct style means that feedback is provided frankly, bluntly and honestly. Negative messages are not softened by positive ones, absolute descriptors are used e.g., totally inappropriate, completely unprofessional and criticism may be given to an individual in front of a group. On the other end of the scale,
negative feedback is provided softly, subtly and diplomatically. Positive messages are used to wrap negative feedback is given only in private. Consequently, when Dutch people (givers of direct negative feedback) receive feedback on papers by Ugandan colleagues (givers of indirect negative feedback) it may appear as if not enough feedback is given by the Ugandan trainers. For the Dutch involved in the training program in Uganda, it may appear that Ugandans feel very positive about the article and only have a minor issue that may need to be addressed. However, this issue might actually be a lot more important than it seems to the Dutch. This difference in feedback style can also have impact on the design and evaluation of a simulation-based team training program that has been implemented in Uganda, based on Dutch expertise. Part of successful learning within these training programs lies in feedback participants receive from the trainers and their peers. To the Dutch involved in the training program in Uganda, it may appear as if not enough feedback is given by the Ugandan trainers and participants or not enough emphasis on what to improve. For the Ugandan participants, the feedback may be clear on how to improve their performances.

Trust

According to the ‘Culture Map’, trust can be built on relationships in business. In task-based cultures, trust is built through business-related activities and work relationships are built and dropped easily, based on the practicality of the situation. In relationship-based cultures, trust is built through sharing personal time and work relationships build up slowly over the long term. Staying in a highly relationship-based society like China for some time without completing any of the intended tasks might therefore seem like a failure for someone from the Netherlands (a task-based society). However, the success is actually in building relationships during this time, and that is essential before being able to start any tasks.

Conclusion and recommendations

National cultures can differ significantly from another, which has important consequences when working internationally. It is important to be aware of your own culture, how it might differ from others and what consequences this can have for your technology or study design. The eight scales of the ‘Culture Map’ can be used as a basis for reflecting on these differences.

To avoid mishaps and to smoothen implementation in other countries, it is essential to involve local staff and to remain flexible and curious.

PIONEERING MEDICAL PROGRESS: A HEALTH COMPANY’S JOURNEY WITH HOSPITAL IMPLEMENTATION

Will Ickenroth, CEO of Nemo Healthcare

There are many areas to consider simultaneously when developing a new product. When analyzing the root causes why most startups fail, technology push is often mentioned. There is a sincere belief of many entrepreneurs that the market will (easily) adopt a new product and is willing to pay a lot of money for it. And this is where things often go wrong, especially when the launch of a new product requires a change in ways of working, training, education, clinical evidence, budget increase and cost reduction. Let’s also not forget that there is great diversity in how healthcare systems work in different countries. Who is the customer? Who are the decision makers? All these factors need to be considered from the start of a development of a new product.

Another root cause is the relatively late response and feedback on a new product of potential users in the market. Clinical studies to investigate clinical outcomes and economical benefits take a lot of time. Of course, approval from a Medical Ethical Committee (METC) is required and the product needs to be safe. But the question, however, is whether it is possible to collect feedback from the market much earlier in the development process of a new product and how to set up shorter clinical studies, covered by the approval of a METC. Could a minimum viable product be defined and approved in close collaboration with potential customers that make it possible to carry out clinical studies and collect feedback from the market much faster? This is certainly an area where close collaboration between industry, hospitals and universities is needed.

Both technology push and late market feedback make it difficult for companies to raise sufficient funding for market implementation. Many companies have limited budget when launching a new product and hope sales will increase revenue quickly. But this rarely happens and companies get in trouble. Proof of concept, clinical and economical evidence and market acceptance are required to get new sources of funding that support the company in growing the business. The earlier a company can mitigate the risks as described above, the higher the chance of getting funding and creating success.

The initiative of eMETC is a good example of a close collaboration between industry, hospitals and university and forms a perfect base for discussing, searching and experimenting with new ways of working.
Design thinking is a non-linear, iterative process that teams use to understand users, challenge assumptions, redefine problems and create innovative solutions to prototype and test. Involving five phases (Empathize, Define, Ideate, Prototype and Test), it is most useful to tackle problems that are ill-defined or unknown.

Many well-known companies have implemented Design Thinking in their daily practice. Examples are Oral-B, GE Healthcare and Netflix. Design Thinking has also found its way into education, where the concept is taught by Design or Challenge-Based Learning. Many universities, both nationally and internationally, are currently using Design-Based Learning as their main type of project-based learning.

Until now, Design Thinking has not been used on a large scale in health care. However, due to many technical innovations in healthcare, the increasing involvement of patients, and the necessity to reduce costs, Design Thinking is increasingly valued as an interesting concept for healthcare.

In the field of fundamental perinatology, Design Thinking could aid in innovative ideas. In fundamental perinatology, research teams are generally multidisciplinary, where the people involved have different backgrounds. Also, the new concepts that are explored are suited to this process. In this article, the Design Thinking process is described using an example from our research group.

Before the concept of Design Thinking can be explained in detail, a brief summary of the example research proposal is given.

Research proposal summary

It is often assumed that many obstetric complications are caused by placenta dysfunction. Fetal growth restriction (FGR), hypertensive disorders in pregnancy and pregnancy loss are some of the complications that can be caused by placental insufficiency. For normal placental function, adaptations to blood vessels have to be made, both on the maternal and fetal side of the placenta. Therefore, it is important that the microvasculature of the placenta is studied. Hence, placenta imaging is discussed. So far, no satisfactory method for placenta function has been used in daily practice. One of the proposed methods is contrast-enhanced ultrasonography (CEUS).

Methods and Results

The Design Thinking process consists of five steps: Empathize, Define, Ideate, Prototype and Test. It is an iterative process, meaning that the process can (partly) be repeated after the fifth step. In this section, every step is explained based on the example of placenta microvasculature imaging.

Empathize - In this phase, the problem is explored. In a human-centered manner, all of the aspects of the problem are investigated. In this way, all of one’s own assumptions are set aside and real insight is gained into the user’s needs. A lot of information is gathered. Different stakeholders and experts in imaging, as well as obstetrics experts, were interviewed in this stage.

Define - The second phase is about defining the problem in a human-centered manner. For placenta vasculature imaging, it is important that the microvasculature of the placenta can be visualized, both on the maternal and fetal side. However, the safety of the mother and baby is most essential when using intravenous contrast agents.

Ideate - In this phase, ideas are generated. The problem is challenged from different directions and insights. The goal is to generate as many ideas as possible in order to eventually select the best ideas.

Prototype and Test. It is an iterative process, meaning that one or more steps are usually repeated because of its iterative character.

At this stage, the vasculature of 16 cases has been shown using CEUS. Next, super localization techniques have been applied to the CEUS images. This led to the visualization of the feto-placental macro- and microvasculature of the cases.

Conclusion

Although still relatively unfamiliar, Design Thinking is a promising and valuable concept for innovations in healthcare. We would recommend implementing this process for future clinical problems with multidisciplinary teams.

To accelerate the translation from research into practice, a multidisciplinary approach is essential. To aid multidisciplinary communication, different tools can be used. One tool popular for innovation in any kind of organization is Design Thinking. This complex thinking process leads to improved and accelerated creative processes, mainly in multidisciplinary teams.

In healthcare research, many steps of the Design Thinking process have already been taken unconsciously, but it helps to structure the brainstorming process. With previous unstructured brainstorm sessions, it is possible to miss out-of-the-box ideas. With the concept of Design Thinking, gathering as many ideas as possible in a human-centered model is key. In this way, input from all viewpoints is secured.

In our field of multidisciplinary and fundamental research in particular, this iterative process could aid in streamlining ideas.

Discussion

Design Thinking has not been used in daily practice in healthcare. However, it is a concept that is very suitable for the implementation of innovations. It is an iterative process, although it is presented linearly in this report.

Within healthcare research, many steps of the Design Thinking process have already been taken unconsciously, but it helps to structure the brainstorming process. With previous unstructured brainstorm sessions, it is possible to miss out-of-the-box ideas. With the concept of Design Thinking, gathering as many ideas as possible in a human-centered model is key. In this way, input from all viewpoints is secured.
IMPLEMENTATION SCIENCE: TRANSFORMING THE LANDSCAPE OF INSURANCE OPERATIONS

Dr. Hans Kuijpens, NZa VGZ Medical Advisor

In the Dutch healthcare system, the medical advisor of a health insurer advises the insurer on whether an innovation is of interest. The primary responsibilities of health insurers in the Netherlands are twofold: improving the quality and availability of care while ensuring its long-term affordability. These objectives can sometimes be at odds.

Dutch Healthcare Structure
- Green blocks in the figure below: laws and regulations.
- White areas: pertain to an individual’s personal responsibility. The central government manages public healthcare through the Public Health Act. Furthermore, individuals are responsible for their own health. If one cannot manage on their own, they are encouraged to consult their network. Three primary support networks ensure access to quality care: 1. Health Insurance Act 2. Social Support Act (WMO) 3. Youth Act (both of which are now managed by municipalities)
- The final block represents the Long-Term Care Act for chronic illnesses.

Highlights of the Dutch Healthcare System
- Cost, quality, and effectiveness should be as transparent as possible.
- Healthcare growth is predetermined.
- Mandatory health insurance; free for those under 18, funded through income taxes.
- Health insurers must accept everyone for the basic package (solidarity principle), and an individual’s health doesn’t affect premium cost.
- The Minister determines the composition of the basic package, with any changes subject to government approval.

Regulatory Authorities in Dutch Healthcare
- Dutch Healthcare Authority (NZa): Definition and tariff setting.
- National Health Care Institute (ZIN): Package content.
- Health and Youth Care Inspectorate (IG&J): Healthcare quality.
- Authority for Consumers and Markets (ACM): Monitors competition and questions insurers about mergers and collaborations. For instance, when hospitals collaborate closely, insurers can offer advice to the ACM.
- Dutch Authority for the Financial Markets (AFM) and Dutch Central Bank (DNB): Due to significant financial stakes, both monitor the system closely.

From Innovation to Clinical Practice
In the Netherlands, innovations often originate from industrial, technical, academic, or pharmaceutical sources. Introducing them to healthcare is more of a hurdle race than a sprint. In 2022, several relevant reports were released:
- Integrated Care Agreement (IZA) and Social Support Act (WMO)
- Health Insurance Act
- Long-Term Care Act

These reports emphasize the importance of evidence-based personalized care. The IZA centralizes “appropriate care”. It also discusses the concentration of complex care and the overall hospital care volume. More healthcare will take place at home, requiring added infrastructure and organization.

Implementing Innovations in Clinical Practice
Questions from the National Healthcare Institute and insurers:
1. Is the innovation truly new or is it part of an existing treatment?
2. If part of existing technology for treatment:
   - Does it improve clinical outcomes?
   - Does it enhance care quality?
   - Does it improve quality of life?
   - Are there no complex changes in costs?

For entirely new innovations, different criteria are considered and stakeholders must decide who should be involved. The Healthcare Institute has set evaluation criteria, indicating that insurers can conduct their evaluations. The ZIN and the NZa are the penultimate steps to approval. This is a crucial document for understanding the path from research to implementation and payment.

For a new therapy, it’s essential to have cost-effectiveness (savings; non-inferiority isn’t enough with rising costs). Interventions must be evidence-based and test performance must be known. For a new diagnostic test, it should be clear if a “new patient group” can emerge (e.g., like with the COVID test).

Every hospital now has an innovation budget 1.5 billion euros nationally; allocated proportionately between primary and secondary care institutions.)
TRANSFORMING CLINICAL PRACTICE: EVIDENCE-BASED STRATEGIES AND TOOLS

Prof. Edwin van de Heuvel, Dean of the Department of Mathematics and Computer Science, Eindhoven University of Technology

Objective
To provide information on the methodology of data collection.

Comparative effectiveness research
This research often involves extensive studies to validate a hypothesis that a researcher is passionate about. An intervention is compared with either a control group or another intervention, assessing both benefits and harms. For this purpose, empirical data related to meaningful health outcomes is collected. There are various methods for this, including trials and observational studies.

Observational studies
They can be roughly divided into:

+ Case Studies: Often the starting point of a research trajectory. They provide a detailed description of a specific case, detailing the circumstances without generalizing the results. There’s no comparison to a control group. Such studies can lead to fresh insights, for instance, unveiling underlying biological mechanisms.

+ Ecological Studies: These studies focus on the characteristics of a group of individuals, often based on location. They establish a correlation or association between aggregated information on the group of individuals (e.g., location) and the group-level health state (e.g., number of symptoms or disease percentage).

+ Cross-Sectional Studies: Sampling data from a population at a single point in time to understand associations between health-related variables. Challenges often include a low response rate and bias in collecting retrospective data, which may reduce representativeness. However, it’s possible to examine multiple variables at a low cost.

+ Case-Control Studies: Similar to cross-sectional studies but sampling is done from two distinct groups: one group has a specific characteristic (i.e., the cases), like having a disease, and one group lacks this characteristic (i.e., the controls) but is very similar to the cases. A drawback is the potential ambiguity in selecting controls, which can cast doubt on how representative the study is.

+ Cohort Studies: Collecting data from a well-defined group that is being monitored over a specific duration, like a birth cohort. Challenges include high costs, difficulties in estimating prevalence accurately if sampling is not involved, and the need for large samples and extended follow-ups, especially with rare conditions. However, being prospective in nature, cohort studies facilitate comprehensive data collection and allow for the tracking of changes over time (estimation of incidence rates).

Each study design has its advantages and drawbacks, as detailed in the table.

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<th>COMPARATIVE EFFECTIVENESS RESEARCH Epidemiological Study Designs</th>
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<td>Association Measure</td>
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<td>Attributable risk</td>
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9
Experimental studies
They typically compare a new treat-
ment or intervention with an existing
treatment or control on human beings.
The control can be no intervention, a
placebo, and care-as-usual. Experi-
mental studies can be roughly divided
into:
  + Clinical Trials: Their objectives
    include the determination of effi-
cacy (treatment works) and safety
(treatment does not harm). Efficacy
does not mean that the treatment is
effective across a broader popu-
lation and on each patient. Safety
is often determined in a trade-off of
benefit and harms. The most
common clinical trial is rand-
omized controlled trials where the
treatments involved are rand-
omized to (groups of) patients.
  + Pragmatic Trials: The goal of
pragmatic trial is to demonstrate
effectiveness (treatment works
under routine conditions). A subset
of pragmatic trials that make use
of cluster randomization (groups of
patients are allocated to the
randomization) are sometimes
referred to as community trials.
  + Field Trials: Experiments on
healthy people grouped by differ-
ent interventions to determine
which keeps them healthiest.

Stages in experimental studies
There are often different stages in ex-
perimental studies to obtain specific
evidence of the new treatment. These
stages are common practice in the
pharmaceutical industry.
  + Preclinical: Animal testing for
efficacy and safety.
  + Phase I: Conducted on healthy
volunteers or sometimes on pa-
tients who have no other treatment
options left in order to determine
relevant doses of the new treatment.
  + Phase II: Focusses on evaluating
biological activity. It usually does not
study clinical events but instead
observes proxies due to keeping
the study size limited.
  + Phase III: Comparative trials
assessing clinical effects.
  + Phase IV: Examines long-term
adverse consequences.

Hierarchy of epidemiological studies
Several medical journals use a spe-
cific hierarchy of study designs to
quantify the importance of evidence
on treatment effects. The most trust-
worthy evidence of treatment effects
is determined with a systematic review,
preferably using randomized con-
trolled trials. This type of evidence
combines multiple studies and there-
fore is most reliable. Second in rank
is clinical trials, since they have more
control over possible biases than
observational studies, particularly
when randomization is applied.
The next type of studies is cohort
studies, since they are mostly pro-
spective and therefore provide real-
time evidence of certain effects.
Case-control studies are then often
considered the most reliable evidence,
since they sample from both the cases
and controls. When controls can be
matched with cases using certain
relevant characteristics of the
patients, this provides a more reliable
piece of evidence than cross-
sectional studies. The lowest levels
of evidence are determined by case-
report studies and ecological studies.
Case-report studies have no general-
izability at all, while ecological studies
only have generalizability at a heli-
copter or aggregated level.

Biases
There are many different biases that
could creep into a study and that
would cause a disturbance in the
estimation of the benefit and harm
of new treatments. Here, we mention
just four of them, often being the
most important biases that can occur
in studies:
  + Selection Bias: The difference
between participants and non-
participants in terms of exposure
and outcome. This would occur
when the process of collecting
participants is affected by factors
that also influence the outcome
and it is usually irreparable due to
insufficient data.
  + Recall Bias: People with different
outcomes might recall and report
information differently. This type
of bias is relevant when retro-
spective information is being
collected.
  + Observer Bias: Judgment can
be swayed by the observer’s
information. This bias may be
eliminated when the observer is
blinded from the treatment.
  + Confounding Bias: The relation-
ship between exposure and out-
come can be disturbed by another
variable, making it challenging to
observe the true effect. Typically
present in observational studies.

Blinding
In clinical trials, it is often recom-
mended to make use of blinding.
First-level blinding is making partici-
pants unaware of the treatment they
receive. This would eliminate the
placebo effect. There is quite some
research on placebo effects through
which it has been demonstrated that
some participants are more suscepti-
able to placebo than others. Second-
level blinding means that the researchers
and doctors are also unaware of who
received which treatment. As we just
stated, this is to prevent observer
bias. It is preferable to include second-
level blinding, but not all clinical trials
can implement this since the treat-
ment cannot be disguised.

Foundation of randomized controlled trials
The most important element in clinical
trial is randomization, i.e., the process
of randomly assigning interventions
to individuals. Randomization is cru-
cial to eliminating confounding bias.
Typical randomization techniques are
complete randomization, random
allocation rule, and permuted block
randomization. Randomization is also
the foundation for demonstrating that
there is a benefit to the treatment.
A randomized controlled trial is, in
essence, a statistical hypothesis test-
ing study. The fundamental test statistic
to demonstrate that there is a benefit
beyond reasonable doubt is called
the permutation test. Based on a
measure of effect (e.g., a mean dif-
ference or odds ratio), the permutation
tests calculate all values of the meas-
ure of effect for all possible permuted
allocations of treatment, which can
also be the outcome for the
randomized controlled trial. The out-
comes of the participants are consid-
ered given, but the treatments are
permuted among the participants.
This leads to a large set of values of
the measure of effect and, when the
observed value of the measure of
effect from the trial is away from this
set, it is unlikely that the treatment
does not contribute.

Issues with randomized controlled trials
Although there is a high level of trust
in randomized clinical trials, they
do pose several huge challenges.
One issue is that there is the vast
variability among people, affecting
generalizability. Other issues include
participants dropping out, non-com-
pliance, and other factors that might
compromise the reliability of randomized
treated trials. These effects aren’t
always considered in the analyses.
Ultimately, the representativeness of
a trial is a question of utmost impor-
tance. There’s often a significant
discrepancy between the research
question, aimed at a population, and
the data resulting from the actual
included population sample.
One study is often not enough. By
pooling data from multiple studies,
you can achieve consistent results,
regardless of whether it’s an RCT or
observational study. In essence,
comprehensive research requires
multiple studies conducted in diverse
settings, and pooling this data offers
more reliable conclusions. However,
this doesn’t mandate the exclusive
use of RCTs; observational studies
can also contribute to this pool.
Thus, we may be much more flexible in
the type of studies that we can use to
demonstrate the benefit and harm
of new treatments. This is also because
causal inference can be conducted
from observational studies.

From efficacy to implementation
There is often a gap in comparative
effectiveness research (CER) where
the focus on process thinking is
missing. Implementing findings into
practice necessitates a process ori-
ented approach. This means:
  + Clearly defining the intended
outcomes of each activity.
  + Identifying and following steps
that facilitate practical implementation.
  + Making adaptations based on
context.
  + Making adjustments based on
accumulated knowledge.
  + Continuously monitoring and over-
seeing all activities.

The overarching idea is that while
efficacy research can highlight what
works in a controlled environment,
the journey to actual implementation
in the real world requires a compre-
nsive, phased, and adaptive strategy
that takes various factors into account.

When adopting a process-oriented
approach, the likelihood of a type I
error might exceed the conventional
5% threshold defined in typical stud-
ies. This risk should be mitigated
through methods such as intensive
simulation studies and the use of dig-
tal twins. There’s a pressing need for
new evidence-based methodological
studies. The emphasis on randomi-
sation might decrease and study de-
signs could be seamlessly integrated
into daily routines. However, this inte-

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**RANDOMIZED CLINICAL TRIALS**

**Methodological issues:** How **representative** is a trial?

- **Population:**
  - Entry criteria: exclusion of individuals’ cause selection
  - Patients enrolled
  - Often live closer to participating centers
  - Must accept trial conditions and consent
  - Error might exceed the conventional 5% threshold defined in typical studies.

- **Trial execution:**
  - Trial execution: missing data, drop-out, and non-compliance
  - Observing and analyzing outcomes of each activity.

  Clearly defining the intended outcomes of each activity.

  Identifying and following steps that facilitate practical implementation.

  Making adaptations based on context.

  Making adjustments based on accumulated knowledge.

  Continuously monitoring and overseeing all activities.

  The overarching idea is that while efficacy research can highlight what works in a controlled environment, the journey to actual implementation in the real world requires a comprehensive, phased, and adaptive strategy that takes various factors into account.

When adopting a process-oriented approach, the likelihood of a type I error might exceed the conventional 5% threshold defined in typical studies. This risk should be mitigated through methods such as intensive simulation studies and the use of digital twins. There’s a pressing need for new evidence-based methodological studies. The emphasis on randomization might decrease and study designs could be seamlessly integrated into daily routines. However, this inte-

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determination complicates statistical analyses, necessitating sophisticated bias correction methods. Frequent interim evaluations become crucial, as does the application of AI and the need to estimate individual causal effects due to population heterogeneity. Future studies should be pragmatic, eliminating exclusive criteria. Moreover, these novel study designs should also provide insights into:

1. **Details of Effectiveness**: This should encompass both a general overview and an understanding of individual outcomes.

2. **Understanding of Causal Effects**: Specifically, understanding the impact of the new intervention in relation to other factors and conditions.

3. **Practical Application**: This would involve insights into how the clinical setting can accommodate or adapt to the new intervention.

Currently, there’s scarcely a trial design that meets all these criteria. Therefore, there’s a compelling case for transitioning to adaptive trial designs. An adaptive trial design is one that allows for modifications to the trial procedures (like dose adjustments) based on interim results. The main advantage of adaptive designs is their flexibility. They can provide a more efficient and ethical approach to determining the clinical benefits of an intervention, especially when there’s uncertainty about the best treatment approach. With the advent of sophisticated statistical software and an increasing emphasis on patient-centric research, adaptive designs are becoming more prevalent. They allow researchers to ‘learn’ from the data as the trial progresses, potentially reducing the number of participants exposed to an inferior treatment and potentially accelerating the clinical development timeline.

**Switch Designs** are often more effective than RCTs since they are immediately implemented in the routine clinical practices. By the end of these studies, evidence is presented to determine whether a particular intervention has worked or not. Data analytic methodology has been worked out in the last decade to effectively make use of these designs compared to more traditional randomized controlled trials. Switch designs can also be more powerful than traditional randomized controlled trials.

**Single Patient Trials**: This approach involves testing multiple treatments within a single patient, searching for the most effective treatment for one person, which can be particularly applicable in fields like psychology. The results of these individual trials can then be aggregated for broader analysis.

**Space RCTs**: Experiments are conducted within a cohort, with every member of the cohort participating in the study. A major advantage of this method is the abundance of control subjects available. A random sample of participants is taken from within the cohort (note: this is different from randomization). As choices are made at various points, multiple groups emerge. This design allows researchers to explore the impact of different attributes, such as an individual’s intrinsic motivation to participate, on the outcomes. This strategy permits both individual matching (to determine individual effects) and comparisons between different intervention groups.

**Conclusion**

The ultimate success of a study is when it culminates in full implementation at the workplace. Naturally, this encompasses all other aspects of implementation science, including understanding the contextual factors, barriers, and facilitators to implementation. It’s essential to take a multi-dimensional approach involving stakeholders, adapting to local conditions, and evaluating both the process and outcomes of implementation. This holistic approach ensures that the findings of a study aren’t just theoretically significant, but they also bring about change. Thus we advocate the development of process thinking in comparative effectiveness research and making use of different studies to accumulate evidence.
Clinical Physics at Máxima MC is responsible for the policy on the quality and safety of the introduction and use of medical technology. The policy’s execution, quality checks, and maintenance are carried out in conjunction with the Medical Technology department. Clinical Physics is always involved in the implementation of new medical technology, including medical software systems.

There is a wealth of (local) knowledge about implementing medical technology in the hospital. Often, a new method is also evaluated after 100 days. But when does implementation become implementation science? According to one definition, implementation science concerns “the study of methods to promote the integration of science concerns “the study of methods to promote the integration of science concerns about implementing medical technology. The policy’s execution, quality checks, and maintenance are carried out in conjunction with the Medical Technology department. Clinical Physics is always involved in the implementation of new medical technology, including medical software systems.

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To implement changes into clinical practice, leaders of change projects are faced with numerous challenges. Examples of challenging implementation programs in pregnancy and childbirth care include the use of a shared electronic medical record system for primary and secondary maternity care, implementing telemedicine and value-based healthcare strategies and many other healthcare improvement initiatives.

In summary

The model for improvement proposed by Langley proposes the use of the three change questions at the start of each cycle of improvement:
1. What are we trying to accomplish?
2. How will we know that a change is an improvement?
3. What change can we make that will result in improvement?

It is advisable to use data-over-time (process control) to monitor the outcomes of your implementation project and to include outcomes that not just show that a technology or strategy is being used but that it has also led to the desired (clinical) improvement.

Critical to the improvement work is working in short, measurable and preferably iterative PDSA cycles to allow for continuous learning. An important element of implementing for improvement is making a sharp distinction between testing and implementation. The essential feature of testing is to reassure the stakeholders that the new change (e.g., technology, protocol) is not implemented before critical adaptations are made. Usually, this is not a one-step approach due to unpredictable real-world barriers and facilitators. For instance, if a clinical trial shows a clear advantage of a new treatment strategy over existing standard treatment, implementing the protocol for the new treatment in your own setting may not show the same effect or may require additional training, resources, etc. This can be easily figured out in short test cycles focused on identifying and improving the factors needed for successful implementation.

Take-home message

An important part of implementation is planning for change. This is best done using a stepwise PDSA-supported process which allows for change leaders to gain trust and adapt to the setting. Well-guided change projects turn adversaries (those who do not trust the new change) into opponents (those who trust you, but are not yet enthusiastic about the change) into allies (high trust, high agreement).
As this e/MTIC Fundamental Perinatology Conference in Lambrey dedicated to implementation science concludes, we reflect on the myriad insights, challenges, and novel ideas discussed. Special thanks to Nadine de Klerk for her excellent chairmanship and to Beatrijs van der Hout for her meticulous note-taking throughout the presentations, which significantly contributed to the development of this book’s chapters.

Each chapter has imparted valuable lessons:

+ The collaborative work of the multidisciplinary PhD team exemplified the synergy between medicine and engineering, underscoring the importance of cross-disciplinary collaboration in research and practical application.
+ Susan Hommerson, a policy officer for medical devices, highlighted the ethical dilemmas in rapidly transitioning clinical device concepts into tangible products, emphasizing the need for careful navigation of these challenges.
+ Medical professionals Arne van Tetering, Kirsten Thijsen, and Ella de Vries illuminated how implementation science can elevate healthcare, particularly in resource-constrained environments, offering hopeful and actionable strategies.
+ Will Ickenroth, CEO of a healthcare technology company, shared candid experiences about the challenges and triumphs of implementing new ideas in hospital settings.
+ Obstetrician Loes Monen and engineer Pascalle Wijntjes advocated for simplifying the application of research findings in real-world healthcare, ensuring that innovations reach those in need.
+ Statistician Professor Edwin van de Heuvel discussed research-supported tools and methods and their potential to revolutionize clinical practices.
+ Obstericin Dr. Bas van Rijn and midwife Hilde Perdok underscored the importance of addressing the difficulties in translating evidence-based practices into healthcare applications.

Collectively, these chapters underscore the transformative potential of implementation science. They call for the adoption of evidence-based methods in healthcare and beyond. As we conclude, let us carry forward these lessons to enhance healthcare and improve patient care.

We hope the insights shared in this book will inspire and guide your endeavors in implementation science.
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