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Closing the cycle of innovation in healthcare in Europe

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Abstract

Pragmatic or practice-oriented comparative effectiveness trials may be conducted to fill the evidence gaps that are revealed after the private sector has performed the trials needed for bringing their product to the market. A tool of increasing importance to identify such evidence gaps is resulting from health technology assessments (HTA) whereby the data derived from clinical research are examined in a systematic manner with reference to effect, safety, as well as additional parameters. Practice-oriented trials are informative for healthcare decision makers, practice-changing and may even be cost-saving for the healthcare payers. There are however only a limited number of funding sources for such trials. Public and private healthcare payers should stimulate the conduct of practice-oriented trials in their effort to maximize patient benefit within the limitation of the available resources. Pragmatic randomized trials can be performed at low cost when based on existing coded electronic health records and as well health registries. Public health decision makers are increasingly taking advantage of results from health technology assessments to support priority setting. In accordance with this it would appear reasonable that decision makers should get more involved in priority setting and funding also in the field of clinical research in order to provide further evidence needed for assessments, reassessments, and subsequent qualified decisions and resource allocations in health care. A closer dialogue and collaboration between the clinical research and HTA communities would facilitate a more efficient utilization of such opportunities.

What is Innovation in Healthcare?

If one asks "What is innovation in healthcare?" one may get totally different answers (1). Researchers who identify a new pathway or overcome a major technical challenge in the development of a candidate drug or device will consider this as innovation in healthcare. On the other end of the spectrum are the researchers assessing the added value of the new drug or device for the patient's health. They do not consider the technical challenges that had to be overcome but merely focus on the patient benefit that can be expected after the introduction of the innovation in the routine healthcare system. In between these two extremes lies an evidence gap. The innovation cycle can be completed by the clinical development, an area largely unknown by the technical innovator and by definition considered incomplete by those who want already to see proof of benefit in a routine care setting.

What clinical evidence do public health decision makers want to see before allowing innovations to be part of the routine care that is covered by the health insurance? A second question is who should generate this evidence, when and how? Options to improve the current situation are discussed.

Split Responsibilities and the Evidence Gap

For medicinal products or medical devices, the implication of governments is typically split between the bodies that grant market access and the (public) healthcare payers, deciding on the coverage under the public health insurance.

For medicinal products, market access in Europe and the US is centrally regulated by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) respectively. It is based on the demonstrated efficacy/effectiveness and safety in typically one or two pivotal randomized clinical trials.

For medical devices, the regulatory hurdle is generally lower and shows more variation depending on the device risk class and the regulatory system (2). In Europe market access is granted by notified bodies through the CE mark. Notified bodies are mainly for profit

entities, accredited by the local government. Even for high risk devices the clinical data set is often limited and typically not made public. In the US, innovative devices need demonstrated effectiveness and safety under the FDA pre-market approval (PMA) procedure. The PMA is often based on a single randomized trial, e.g. comparing a new invasive procedure versus a sham procedure. In contrast to Europe, the evidence is typically reviewed during a public expert panel meeting. The different approaches in Europe and the US result in devices coming on the European market earlier but often with way too little clinical data to do a clinical assessment of patient benefit.

The EU directives for medical devices remained very vague on clinical development and did not provide a real handle for the notified bodies. In May 2020 they are replaced with new EU regulation which includes the requirement to demonstrate clinical benefit versus state of the art. This could be interpreted as a requirement for a comparative trial versus the best available alternative, but it remains to be seen how this is put into practice.

The split in objectives and responsibilities of the two bodies, the regulators and the payers, linked to one and the same government is one of the reasons for the growing evidence gap remaining after the private sector has performed the trials needed for bringing their product to the market.

Whereas the process of bringing medicinal products or devices on the market is now centralized in Europe, this is not at all the case for the pricing of medical products and their coverage by the healthcare payer. Healthcare is still a national competence in Europe, with even varying forms of regional autonomy within one country. Aiming at a justified and fair coverage of new and sometimes high cost interventions, the process of health technology assessment (HTA) was developed over the past decades to advise healthcare payers in the decision making. Fortunately, regulators and HTA bodies or payers on both sides of the Atlantic have facilitated parallel scientific advice with companies embarking on long and costly confirmatory trials (3–5).

National and regional HTA bodies want to assess the added patient benefit and the value for money proposition of the new intervention in the local routine care setting. The evidence gaps identified during HTA may be important as there is no regulatory requirement to assess the added therapeutic value and the comparator used in the confirmatory trials may not reflect best practice. This is a point where industry, regulators, and HTA bodies tend to disagree during early dialogues (6). In addition, the very young and the very old or frail elderly tend to be excluded from registration trials. However, they may be most in need of better treatment and make up a considerable part of the target population.

How to Reduce or to Fill the Evidence Gaps?

Obviously the most direct way to reduce the evidence gap would be to align the decision making by regulators and HTA/payers. The pre-market phase offers a unique opportunity to compare the innovation versus standard of care, evidence which is unlikely to be generated after marketing authorization.

This would mean the "best available alternative" is used as one of the comparators in the pivotal trial(s) (7). Currently, a direct comparison of the new intervention with this "best available alternative" is often not available when a medical product is proposed for reimbursement, hampering the evaluation of added therapeutic benefit (8), and the development of a valid cost-effectiveness model. Furthermore, it is important that the real target population is sufficiently represented and that the primary endpoint is a patient-relevant outcome.

A second best approach would be to fill the evidence gaps identified during horizon scanning efforts by payers or during HTA, by conducting the missing randomized comparative trial immediately after regulatory approval. With the exception of England, evidence gaps identified during HTA evaluations are however rarely suggested to local trial funders as a trial topic or to medical societies defining a research agenda in collaboration with patient organizations.

Local healthcare payers are not in a strong position to demand a head-to-head comparison sponsored by industry, while for patients, healthcare workers, and payers the resulting information can be crucial for decision-making.

Payer decisions of so called "coverage with evidence development" (CED) mostly remain limited to data collections using registries. Only exceptionally, the evidence thus generated is hard enough to decide on the continuation, discontinuation or restriction of coverage. It can even be considered a bit naïve to expect a company to voluntarily generate data that might put the reimbursement of its product at risk.

More informative and possibly a better investment of public money is a publicly-funded practice-oriented comparative trial. Such a trial may even be included under a CED as is being explored in Germany (9). Practice-oriented, also named practical or pragmatic trials, recruit a broad patient population, reflecting routine care, and are therefore quite informative to healthcare decision makers (10). Practice-oriented trials have proven to be practice changing in areas ranging from neonatology (11) to oncology (12) and may even lead to regulatory actions as seen after the 6S trial (13).

Randomized Clinical Trials as an Essential Part of Medical Research

Public funds account for about US$ 100 billion or about 30 percent of the global investment in healthcare research (2012 data) (14;15). In Europe, public spending on healthcare research is US$ 53 per capita, much lower than in the US with US$ 154 per capita spent (2014 data) (16).

Clinical trials are an essential part of healthcare research with only a limited number of public funding sources (17;18). Despite all possible matching and correction algorithms applied on observational data, randomized clinical trials (RCTs) remain the cornerstone for the generation of clinical evidence, as randomization also balances for unknown factors. Early phase exploratory trials are a natural continuation of academic basic and translational research efforts in a development cycle and account for the vast majority of trials registered in ClinicalTrials.gov (2007–2010 data) (19). In general, molecules or devices developed in an academic setting are passed on to the private sector for further development, in return for some royalties in the case of commercialization.

For drug repurposing and interventions not controlled by industry such as surgical techniques, radiotherapy, exercise and physical therapy, psychotherapy, diet, or non-commercial software tools assisting in medical decision making, there may be a need to fund with public means not only comparative effectiveness trials but also the full clinical development (17–20). A European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) was set up to provide advice and expertise to the Commission services in relation to the implementation of the EU Pharmaceutical legislation, as well as

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programmes and policies in this field. New developments in the STAMP working group of regulators and pharmaceutical industry point to the possibility for regulators to extend (and not only restrict) the label based on publicly-funded trials for repurposed drugs (21).

In addition to the benefit to patients, funding clinical trials with public money may have a positive return on investment (11;17). Key elements for success of publicly funded trials are a solid selection process, a professional conduct of the trial and the swift implementation of the findings in routine care (11;17). The trial selection process has to check the need for the evidence as well as the methodological quality of the proposal. Patients are best placed to suggest the needs to be addressed as well as to judge the burden of participation. Study endpoints need to be patient-relevant and initiatives are ongoing to standardize such endpoints for a large number of medical disorders (22).

Public and private healthcare payers should stimulate the conduct of practice-oriented trials in their effort to maximize patient benefit within the limitation of the available resources. However, to our surprise, healthcare payers in Europe may not be allowed, have never considered or are even not interested in funding clinical trials. Despite the potentially high efficiency gains for the healthcare payers, we did not succeed to convince a sufficient number of healthcare payers to co-fund a large international trial on immunotherapy duration in melanoma.

While clinical and health policy decision makers increasingly take advantage of health technology assessments, there is accordingly a need to promote their involvement in all aspects of clinical research, including priority setting, infrastructure development, and funding (23). Relatively few funders of healthcare research aim for efficiency gains, and are associated with healthcare systems or healthcare payers. In many countries funding streams for healthcare research are embedded in education and research departments, sometimes totally disconnected from the healthcare systems in the country (17).

The largest public funder of health research is the National Institutes of Health (NIH) in the US (18), which used not to focus on pragmatic clinical trials (23). A positive evolution may be the consideration by the FDA of real world evidence generated using more pragmatic randomized clinical trials (24). A point of attention remains the inclusion of an appropriate measure of treatment adherence in such trials.

In Europe, the European Commission, through the Scientific Challenge "Health" framework, is co-funding a number of multinational clinical trials but only a subset of which can be categorized as truly practice-oriented. In England, a substantial part of the National Institute for Health Research (NIHR) expenditure is invested in clinical trials, mainly large practice-oriented trials being part of the NIHR HTA programme (25). In addition, The Netherlands Organisation for Health Research and Development (ZonMw) (17) and more recently also the Belgian Healthcare Knowledge Centre (KCE) (26) provide funding for practice-oriented trials that benefit patients and have the potential to increase the efficiency of the healthcare system. For trials of relevance for clinical practice in both Belgium and the Netherlands a first common international call (BeNeFIT) was launched in 2018 (26). In Germany, new legislation allows such trials to be part of a CED scheme (9). In order to avoid research waste, funders of trials have an interest to share information on trials they plan to fund. In addition, international collaboration between funders of clinical trials, right from the selection process, seems to be key to facilitate synchronization of the funding of large international trials. This was recently proposed by the ERA-net on rare diseases that launched a call in 2016 to fund European multinational repurposing trials through combination of national funding. Further development of international, cross-continental funding schemes is on the agenda of the Clinical Research Initiative for Global Health (CRIGH) (27).

Delivering a High Quality Trial on Time and within Budget

The prices of new drugs have increased in a way that may not be sustainable, even in developed countries. Few options are available to change the system (28;29). Most are very fundamental and cannot be realized in the short term. A less drastic change could be to require companies to demonstrate (or at least assess) added therapeutic benefit for their innovative drug or device as discussed above.

Despite reportedly being one of the reasons for the high cost of new drugs seen today, publications detailing the cost structure of a clinical trial or a clinical development programme remain very scarce. A systematic review on the topic did not identify a single publication detailing the costs and resource use for the various clinical trial activities (30).

The median cost of a phase 3 pharmaceutical trial is US$21.4 million (data 2010–2015 from seven major pharmaceutical companies) (31). For pharmaceutical trials in the US (2004–2012 data), the average cost of a confirmatory trial (phase 3) ranged from US$ 11.5 million (dermatology) to US$ 52.9 (pain and anaesthesia) on average (32). In comparison, the average cost of 28 phase 3 trials funded by NIH in the field of neurology was nearly 12 million USD (33).

For academic trials clinical trial units in universities or large hospitals may assist researchers with the design, budgeting, and conduct of clinical trials. Such clinical trial unit networks received public funding to get started in Germany or continue to receive NHS funding in England (17).

Not only the overall trial budget but also the way funds are released during a trial is a determinant of successful delivery. At KCE and ZonMw, the costs for the organization of the calls, the coordination of expert review of the trial proposals and their budgets over multiple selection rounds and the close follow-up of trial progress, can roughly be estimated at 10 percent of the total payments made for funded trials. Public funds for clinical trials are often spent using fixed amounts paid out on predefined dates, independent of the progress of the trial. In line with industry practice, a fee-for-performance principle, accomplished through reimbursement for completed case report forms, allows public funders to more easily cope with delays in recruitment or the need to open additional sites in a large trial (34). In the KCE Trials programme, a publicly available trial budget tool is used to try to achieve a correct and consistent amount for specified tasks across all funded trials (35). For payments, the fee-for-performance principle is applied, not only for site payments but also for the sponsor-related activities. A non-reimbursable advance for preparing a full proposal as well as for the site feasibility check will reduce the risk for both applicant and the funder (35). Trial registration in a publicly available registry before the start of recruitment is required. The final payment is made when the manuscript with the study results has been submitted for publication, thus stimulating the publication of the results for all trials. Finally, trial funders should foresee a process of data sharing to be able to reuse the trial data for research purposes (36). The creation of standards for this principle is a challenge that has to be addressed at national, European, and international levels.

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Currently up to half of all molecules fail in phase 3. Adaptive pathways aim to significantly reduce time to market. There is a risk that drugs thus enter the market that would have failed in a full phase 3 programme. In such cases, a real-time direct capture of safety signals should ideally be based on coded electronic health records, e.g. using SNOMED. However, also randomized pragmatic trials could be performed more efficiently if based on coded electronic health records or high quality registers.

As an example, in Norway all health regions have been running projects to develop novel electronic systems in the specialist health care for real-time registration and monitoring of treatment and outcomes at the patient level. Records, shared between hospital and ambulatory care, could then act as the foundation for randomized trials answering additional effectiveness and safety questions.

Meanwhile, registry-based randomized controlled trials piggybacking on existing quality registries, as in Sweden, have proven to offer a fast, robust, and affordable way to generate real-life evidence (37). Compared with a traditional RCT studying coronary thrombectomy and costing US$ 15 million, a very similar registry-based randomized controlled trial in Sweden showed a faster recruitment and had a price tag of only US$ 0.5 million (37).

A Need for Increased Interaction Between the Clinical Research and HTA Communities

Health technology assessments may offer a systematic tool for the identification of evidence gaps in clinical research. Thus, there is a potential to use such information in a more efficient way to feed into the processes of defining further relevant research questions. In order to facilitate this mechanism, there is a need to promote a closer collaboration between the clinical research and HTA communities, which may promote the conduct of more pragmatic trials in particular as well as research in general along the whole developmental pathway of novel and improved treatment options. In addition, both clinical research and HTA environments face several similar challenges, for example related to the potential use of real world data, extending the evidence platforms in both fields. However, there are critical issues related to quality assurance of such data which would benefit from collaboration between clinical researchers and HTA experts. In the long term, an increased interaction between clinical research and HTA may pave the way for an increased involvement from decision makers in health care in priority setting and funding. Results from a survey among HTA agencies indicate that this interaction is already taking place in England with NICE providing research questions for NIHR funded trials. Lessons learned there should be taken into account, making sure the funded trials address the research questions timely and properly.

In the CRIGH (27) launched in 2017, as a follow-up to an initiative from Organisation for Economic Co-operation and Development to facilitate international collaboration in non-commercial clinical trials (38), projects have been included addressing major challenges in the field of clinical research as well as comparative effectiveness research. This may represent one contribution to approach the issues raised here.

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