Register or electronic health records enriched randomized pragmatic trials: The future of clinical effectiveness and cost-effectiveness trials?

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Abstract: For many interventions in health care, there is limited information on efficacy, safety and cost-effectiveness even long after they have been implemented. To decide between treatments, the randomized controlled trial (RCT) provides the strongest evidence. This creates a problem because RCTs are very expensive, logistically challenging and generally cumbersome. Observational studies are inexpensive, but create weaker evidence. The pragmatic randomized trial, enriched with routinely collected register or electronic health record (EHR) data may be a solution to this dilemma since they are much less costly than traditional RCTs but create much stronger evidence than observational studies. Pragmatic randomized trials mean that patients in routine care are randomly allocated to alternative treatments. The outcome of the treatment is then followed up in existing registers with patient data. This means that it is possible to 1) follow patients in the normal care situation - unlike the often artificial situation in the traditional RCT, 2) that the costs are low, even for large studies and 3) that a broad spectrum of outcomes, including both health and economic outcomes, can be collected. Pragmatic randomized trials using register or EHR data in principle lend themselves well to health economic evaluations. We have identified a number of such trials in the literature. Very few, however, include economic outcomes.

JEL Classification: I100, I190

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1 Introduction

Each day, a myriad of large and small decisions are made in health care. These decisions are based on some idea of the advantages and disadvantages of the various options available. If information about the various options' impact is uncertain or inaccurate, there is a risk that the decision maker chooses a suboptimal option. For many interventions in health care, there is unfortunately very limited information. It was for example noted in one paper that "*we still do not know which treatments are useful for acute stroke, but if every patient in the world experiencing a stroke were admitted to trials we would have enough patients within 24 hours to answer many of these questions*" (Smith and Chalmers, 2001). Instead, even long after an intervention has begun to be used, there is often a lack of knowledge about the

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efficacy and safety compared to relevant alternatives (Smith and Chalmers, 2001; Tunis et al, 2003; van Staa et al, 2012). Both the Swedish Council on Health Technology Assessment (SBU) and the National Institute for Health and Care Excellence (NICE) in the UK have created databases with hundreds of documented knowledge gaps regarding treatments that have been used in routine health care for years or decades (see www.sbu.se and www.library.nhs.uk/duets).

Information is valuable because it reduces the expected cost of uncertainty by reducing the probability of making the wrong decision. It would be easy to conclude that more information is always better. If there is no cost associated with acquiring additional information, this is also the case. But as a rule, information is costly. According to some sources, phase 3 trials of pharmaceuticals cost up to \$40 000 or more per patient (Cutting edge information, 2011). Therefore, the value of the additional information has to be weighed against the cost of acquiring it. At least in theory, there is thus an *optimal* amount of information in each decision situation (Claxton and Posnett, 1996).

In evidence based medicine (EBM) there is a rather clear hierarchy of evidence in which the highest form is the randomized controlled trial – the RCT. The randomization assures that both known and unknown confounding factors are evened out between groups and the control treatment assures that the intervention is different than the natural progression. We usually find the observational study much further down on the evidence ladder. Without randomization, tests of efficacy are much less credible. This creates a problem because RCTs, which create strong evidence, are very expensive and generally cumbersome. The logistics of an RCT are challenging, the recruitment process complicated, staff needs to be trained and the study sites monitored. Observational studies are inexpensive, but create weaker evidence. The pragmatic randomized trial, enriched with routinely collected register data, may be a solution to this dilemma. Since they are much less costly than traditional RCTs but create much stronger evidence than observational studies, register-enriched pragmatic trials create a shift in the optimal amount of information so that much more information becomes optimal.

One area that is particularly underserved with knowledge from RCTs is data for economic evaluations of various treatment options. Looking at reports from, for example, SBU or NICE it is not unusual that there is not a single study of cost-effectiveness included in a systematic review, either because none have been published or because the ones that have do not meet even the most basic quality criteria.

To support better decision making, resource use data and costs used for analyzing cost-effectiveness must reflect daily clinical practice. There are several reasons why traditional RCTs seldom generate data ideal to study the cost-effectiveness of various treatment options. Traditional RCTs are rarely intended or designed to study cost-effectiveness and are not powered to show differences in resource utilization. Since the distribution of costs is typically skewed and truncated at zero, many more patients may be needed to show differences in cost than in efficacy (Briggs and Gray, 1998). There is also a problem that RCTs typically have very carefully selected patient populations, e.g. without co-morbidities. Small and selected populations are efficient and ethical from a regulatory standpoint since fewer patients need to be included in trials, but this makes the external validity of the trial questionable in many cases. Traditional trial protocols are also often very different from how actual patients will be treated in routine health care, not least in that the choice of comparator often does not reflect clinical practice. Measuring resource consumption becomes difficult also because many costs are driven by the trial protocol, i.e. the resource use is mandatory within the trial (e.g., a certain number of office visits).

The purpose of this article is to give an introduction to pragmatic randomized trials, analyse their strengths and weaknesses and from a policy perspective discuss facilitators

and barriers to their use. Finally, we also present a review of randomized pragmatic trials with follow up in electronic health records or registers. We aim to also describe if they are used to study economic outcomes. To the best of our knowledge, no systematic reviews of these trials have been published. Although not systematic, our review may be the most comprehensive in the literature to date.

2 The pragmatic trial

A lot of questions in health care go unanswered because RCTs are so expensive. In 2001, Smith and Chalmers (2001) wrote an article in the *British Medical Journal* about their vision for medical research in the new century. They wished both easy access to high quality reviews of evidence for various interventions, and streamlined recruitment to randomized trials as part of routine medical care whenever there is uncertainty about the effectiveness of the treatment options. The availability of systematic reviews is now generally good, but pragmatic trials in routine care continue to be rare. Instead, there are many examples of almost irrelevant comparisons with placebo, and studies conducted in homogeneous patient populations that do not reflect the real target population (Tunis et al, 2003). In 2003, Tunis et al (2003) described that the widespread gaps in evidence-based knowledge was a sign of systemic deficiencies in the mechanism for evidence generation in the United States. They suggested that the U.S. should create an infrastructure to implement pragmatic trials in the healthcare system. Their proposal was partly based on a publication by Schwartz and Lellouch (1967) from over 30 years (!) before. The purpose of pragmatic trials is to generate the knowledge needed to make informed clinical decisions. The main characteristics of a pragmatic trial were described by Tunis et al (2003) in four points:

1. **Relevant comparators - with the potential to change clinical management**
Instead of placebo comparisons, active interventions should be tested against each other.
2. **Broad population - to reflect the actual patient population concerned**
The patient population examined should reflect the patients seen in clinical practice. This is in contrast to most traditional phase 3 trials which often use strict inclusion and exclusion criteria to define the study population.
3. **Heterogeneous settings**
Patients should be recruited from the units where they actually receive treatment. This contrasts to conventional clinical trials, which are generally conducted at university clinics.
4. **Broad range of outcomes**
Outcome data collected should reflect not only the mortality, morbidity and disease-specific dimensions, but also quality of life and cost outcomes.

From point 4, we believe a fifth point follows:

5. **Sufficient follow-up.**
To assess effects such as mortality, unusual side effects and cost, significantly longer follow-up than standard RCTs are required.

A randomized pragmatic trial in the sense we mean here is performed by randomizing patients in routine health care. The randomization instrument may be over the phone, internet or embedded in the electronic health record (EHR) or in a disease register. Another randomization technique which is sometimes used is cluster randomization in which health

care units rather than single patients are randomized to use one treatment or the other. Data collection in the trial is pragmatic and is done through data sources that are collected anyway, irrespective of the trial. Such data is typically found in EHR, disease registers, other registers or a combination of these sources. Hybrid forms exist in which some data are collected at the clinical site from the patient and other components collected in registers. The usual ethical and formal regulations apply for these studies.

In fact, this design allows the researchers to collect data that are particularly well suited to study cost-effectiveness. There are four main reasons why pragmatic trials create evidence with relatively high validity for decision makers concerned with a cost-effective use of health care resources. First, a clinically relevant comparator is used. Second, patients in the trial represent the patient population in which treatments will be used rather than the often highly selected patient populations in regular RCTs which are filtered through strict inclusion and exclusion criteria (Bombardier and Maetzel, 1999). Third, outcome data relevant for cost-effectiveness analysis, such as quality of life and cost are collected. Fourth, the trial is conducted in routine care which means that costs are not driven by the study protocol. Fifth, follow-up is long, as register-based outcome assessment is performed separate from the trial, many times until death. Furthermore, trials can potentially be powered to detect differences in cost and quality of life without being prohibitively expensive or cause difficult ethical dilemmas. Together this will not eliminate, but certainly reduce the need for modelling in health economic evaluations. Since the trials are prospective, it will take some time to collect the evidence so especially in early stages modelling will still be necessary.

3 Obstacles for pragmatic trials

There are practical as well as technical, bureaucratic and economic obstacles that slow the expansion of pragmatic trials. Here we will present some of these obstacles.

3.1 Lack of relevant records

Tunis et al (2003) pointed out that there must be an infrastructure for health data that facilitates the implementation of pragmatic trials. Some countries, or health care systems, already have access to a relatively good data infrastructure for many diseases. The Nordic countries stand out in this respect with access to national health data for the entire population and nationwide registers for a number of disease areas. This type of infrastructure for health data dramatically lowers the cost of data collection for both pragmatic trials and observational studies. Most countries still lack such infrastructure.

In Sweden, there are a 100 or so disease registers (called quality registers) covering a wide panorama of care areas, from dentures to diabetes and HIV. There are also registers covering sick leave and disability pension, kept by the Swedish Social Insurance Agency. Furthermore, there is a national cause of death register and six national health data registers: the cancer register; the prescribed drug register; the national patient registry; the medical birth register; dental health registers and a register for municipal health care to the elderly and persons with disabilities. Health data registers are regulated and healthcare providers are required to report back to them. They therefore have almost complete coverage in their areas (although there are gaps, particularly in reporting from private providers) and also have long time series. Health data registers do not cover the entire health system. There is currently no statutory support to collect data from primary care or non-medical interventions in specialist outpatient care. This is a problem because about half of all physician visits in outpatient care is provided in primary care. Furthermore, they do not always contain information on disease-specific health outcomes and are therefore sometimes insufficient to

study treatment of a specific disease. Quality registers, on the other hand, are often more suited to follow the progress of a particular disease based on health outcomes, but have other limitations. The quality registers that exist cover only a quarter of health care costs in Sweden (Rosén, 2010). For many health care interventions and care areas there are no registers. Some registers are of a very high quality, but many others are not in terms of coverage, data quality, timeliness and relevant outcomes. It can be difficult to access data from quality registers. The primary purpose of quality registers (according to the Patient Data Act) is continuous improvement in healthcare and registrars are not always willing, or able, to disclose data for research and other purposes.

Thus, even in Sweden there are large gaps in the data. However, disease and health data registers may not be the only way forward. The so called “big data revolution” points instead to directly using electronic health records. Yet, there remain many questions about e.g. data quality and collecting relevant parameters within the electronic health records (van Staa et al, 2014).

3.2 Records may lack relevant outcome data

Sometimes the records do not contain data on all outcomes of interest. One example is health-related quality of life used in, among other things, health economic evaluations of interventions. Another example is data on absence from work and other cost data needed to capture indirect costs. Many other so-called “soft” outcomes are not available in registers or even medical records. This means that the study may have to proceed without these variables or alternatively invest in a separate collection of these data.

3.3 Funding - who should pay?

An obvious obstacle to expansion of pragmatic trials in routine health care is funding. Compared to traditional randomized trials, pragmatic register-based trials significantly lower expected costs, but they are of course not free. Costs include implementation of a system for randomization, time for obtaining informed consent and training of physicians and other health care professionals involved.

Moreover, pragmatic trials require both administrative and analytical resources (biostatisticians, epidemiologists, health economists). Such an organization must be built and staffed.

Traditionally the pharmaceutical industry has been financing drug trials and it will be a challenge to change this. However, we note that the cost in the end, of course, already is borne by those who purchase pharmaceuticals - the pharmaceutical industry has no other source of income that can finance trials.

3.4 Rules and principles for research must be reformed

Currently, it is compatible with good medical practice to more or less arbitrarily choose intervention A or B for a particular patient group if there is uncertainty about the interventions' relative effects, safety profile, and cost (van Staa et al, 2012). At the same time it is not consistent with good research practice to allow the doctor to randomize the same patients to either intervention A or B unless comprehensive information is provided and patients give informed consent. In both cases, patients face the same risk to receive a suboptimal treatment. The difference is that in the latter case evidence is generated over time, which would benefit future patients. Moreover, it could be beneficial also for the randomized patients in the case of treatment for a chronic disease or a condition that may recur.

3.5 Risk of intrusion of patient privacy

Linking of different data sources is always fraught with the danger (real or perceived) of a violation of privacy. A study design without linking data from different sources cost more and is likely to give data of lower quality, but reduces the risk of a violation of privacy. This problem is not unique to register-enriched pragmatic trials, but also arises in register-based observational studies and must be weighed against the value of generating knowledge.

To minimize these risks, participation should be voluntary, either through the application of an *opt-out* system or an *opt-in* system, which is the rule in conventional clinical trials. Furthermore, additional safety measures should be taken at the analysis stage by the involved scientists. They should have access only to anonymized data and only report results at an aggregate level.

3.6 Drawbacks with double un-blinded trials

Pragmatic trials may use both un-blinded treatments and un-blinded outcome measurements, for both patients and therapists. This means that in the un-blinded situation patients' and physicians' expectations of the various treatments can interfere with results. At the same time, these expectations can be assumed to exist also in the clinical reality that the trial results will be implemented in. This is sometimes cited as a motive for having un-blinded treatment that maintains "*the ecology of care*" (Ware and Hamel, 2011). In addition, it may lower the barrier to recruiting both patients and medical staff, who may feel uncomfortable with blinded treatments (van Staa et al, 2012). Outcome measurement however, can and should preferably be done in a blinded fashion, which is often the case by default when register-based outcomes are collected. Furthermore, blinded outcome measurement may be irrelevant in some cases, such as when mortality is used as outcome measure.

3.7 Risk of selection bias

Furthermore, also pragmatic trials face a risk of patient selection bias regardless of how efficiently data may be collected or how wide the inclusion criteria are set. Ultimately it is the patient and the doctor who decide if a particular patient will enroll in the trial or not. They may perceive that a certain treatment is superior for that particular patient and thus unwilling to take the risk involved in a randomized trial. This problem is not unique to pragmatic trials - it is in fact, as we have argued- a smaller problem than in regular RCTs.

4 Opportunities with pragmatic trials

Pragmatic, register-based studies open the possibility of making randomized head-to-head studies on a large scale, instead of placebo-controlled trials with limited generalizability or observational (that is, non-randomized) studies, which may be influenced by both known and unknown confounding factors. Thereby, high-quality evidence of good generalizability can be generated at an affordable cost. Since there is very little in terms of overhead activities compared to usual clinical practice, costs can be kept as low as \$40-50 dollars per patient in large trials (Huang et al, 2013; Lauer and Bonds, 2014). Part of the uncertainty in clinical decision making could be reduced using pragmatic, register-based studies employing routine care and routine collection of health data. Opportunities that may possibly be created with pragmatic trials include:

- Generating high-quality evidence with good generalizability from head-to-head studies
- a much lower cost than traditional trials

- reducing the arbitrariness of many treatment decisions
- patient benefit through faster evaluation of which treatments are best for which patients
- capturing the value of treatments in routine care
- generating data useful for cost-effectiveness assessments

5 Experiences with pragmatic, register-based trials

There are already several examples of pragmatic trials that are fully or partially dependent on retrieval of outcome data via disease registers and linking with other data sources. In Table 1 we list 12 trials we have identified. Below we discuss some of them in more detail and then discuss experiences with pragmatic trials in three countries, the US, UK and Netherlands.

5.1 Examples of pragmatic trials

Electronic health records and registers have been used to complement data collection in clinical trials for some time. Although not randomized, the Swedish Obese Subjects (SOS) study of bariatric surgery versus conventional obesity treatment, started in 1987, has used it for, e.g., analysis of mortality (Sjöström et al, 2007), cardiovascular events (Sjöström et al, 2012), cancer (Sjöström et al, 2009) and long-term health care use (Neovius et al, 2012). The Scandinavian Simvastatin Survival Study (4S), used the cause of death registry and cancer registers (Strandberg et al, 2004). Similarly, a pragmatic randomized trial of an in-hospital clinical pharmacist service used electronic health records and the prescribed drug register in Sweden to supplement data collected on-site to assess cost-effectiveness (Wallerstedt et al, 2012). The Standard Care Versus Celecoxib Outcome Trial (SCOT) is a trial in which electronic health records are used for patient identification and follow-up but research staff rather than clinic staff assess eligibility and recruit patients (McDonald et al, 2013).

TASTE - Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia is one of the most ambitious register-based, randomized trials that have been performed to date. In this trial 7 200 patients were recruited to evaluate two different treatment strategies in myocardial infarction in routine care (Fröbert et al, 2013; Lagerqvist et al, 2014). The primary outcome, mortality, was obtained via linkage to the causes of death register. Virtually the only extra work was the randomization, bringing the cost of the trial down to an estimated \$50 per randomized patient. In addition, recruitment was very fast. When the study was published it was described in an accompanying perspectives article as the potential next disruptive technology in clinical research (Lauer and D'Agostino, 2013).

REDUCE MRSA - Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA had even more patients than TASTE, 74 256 from 43 hospitals and used cluster randomization and data from data warehouses. Infections in intensive care units is a very important clinical problem, but there is controversy regarding which method to use for prevention. In the study, the researchers therefore compared targeted versus universal decolonization. The study gave a conclusive answer to the clinical question at the remarkably low cost of \$40 per patient (Huang et al, 2013).

SWEFOT- *Swedish Pharmaco-Therapy Trial* is a small, randomized clinical trial in rheumatology comparing biological and non-biological combination therapy as second-line treatment for patients with rheumatoid arthritis (RA) who show insufficient response to

standard treatment with methotrexate alone (van Vollenhoven et al, 2009, van Vollenhoven et al, 2012). This is a common decision situation in the treatment of RA where there is limited scientific evidence concerning which treatment option is cost-effective. The study's primary outcome measures of disease activity, was collected in a disease register. A large number of cost outcomes were collected through linking with registers at the National Board of Health and Welfare and the Social Insurance Agency (Eriksson et al, 2013a; 2014). At one-year follow-up, patients randomized to biological treatment were doing better on measures of disease activity than the control group. However, this difference did not remain statistically significant after two years. As for health-related quality of life and lost workdays, there was no difference between the groups at either one or two years (Karlsson et al, 2012; Eriksson et al, 2012). Regarding both drug costs and non-primary outpatient care costs, the biologic group incurred significantly higher costs (Eriksson et al, 2014).

Experiences in the US, UK and Netherlands

Pragmatic trials were recognized as a promising area in the U.S. already 12 years ago in the *NIH Roadmap: Reengineering the Clinical Research Enterprise* (NIH 2002). However, the general lack of supportive health data infrastructure was recognized as a problem. There have been a few randomized pragmatic trials conducted in the U.S. since. The REDUCE MRSA was discussed above. Another inventive study is the MI-FREEE which randomized patients to either full or usual pharmacy coverage after myocardial infarction to investigate adherence to preventive drug treatment (Choudry et al, 2011). The NIH Collaboratory must also be mentioned. It is a project devoted to promoting pragmatic trials utilizing EHRs as data sources and building a new national infrastructure for collaborative research. The Collaboratory's cornerstone is a series of demonstration projects – currently 10 projects are listed - that will utilize EHRs as data sources across multiple institutions and health systems.

Some pragmatic trials have also been conducted within the Veterans Affairs (VA) health care system, which has comparatively good health data, even if the records only include a selected group of military personnel, and may also not include all health care the patients consume (Roehr, 2013). Pilot studies are underway on treatment of hypertension, treatment of diabetes, mental illness and HIV (Roehr, 2013; Fiore et al, 2011). The Veterans Affairs are also pioneering methods in which they adapt the probability of randomization to the different treatments over time once the evidence starts to build up in the system (Fiore et al, 2011). This means that they can automatically begin implementation of the winning strategy, which further lowers the barrier to convert research results into clinical benefit (Roehr, 2013). Furthermore, the VA's automated systems will be used to assess eligibility and present the possibility of randomization to the clinician at the point of care (Fiore et al, 2011).

As in Sweden, the UK has identified a large number of knowledge gaps in health care, many of which could be filled in with the help of pragmatic trials. In contrast to Sweden, the UK has a nationwide registry for primary care (*Clinical Practice Research Database; CPRD* (formerly GPRD)), comprising approximately 5 million individuals, or approximately 8 % of the population (Roehr, 2013; van Staa et al, 2012). Several pilot studies in the form of pragmatic trials are now underway based on CPRD, including Retropro and eLung (Table 1). The primary objective of these studies is to evaluate the feasibility of conducting point-of-care trials using routinely collected data (van Staa et al, 2014). The studies are based on recruitment at first treatment contact when informed consent is obtained and randomization occurs (van Staa et al, 2014). Then the patients are followed in routine care through the existing electronic medical record system. The trials have rationalized away blinding to avoid complicating factors for health care providers and

increased costs. It has been an explicit goal to gain acceptance from general practitioners, who have made it clear that minimization of extra administration is crucial (van Staa et al, 2014). However, this has not yet worked so well in practice. The governance approval process for the two studies took over 3 years. Nearly 60% of the practices (n=270) expressed interest in participating in the Retropro and eLung studies but the number of interested practices dropped substantially with each stage of the governance process. In Retropro, 6.5% of the practices (n=30) were eventually approved and 3.7% (n=17) recruited patients; in eLung, these numbers were 6.8% (n=31) and 1.3% (n=6) respectively. Retropro successfully completed recruitment (301 patients) whereas eLung recruited 31 patients. Good Clinical Practice guidelines, governance and consent procedures substantially affected the intended simple nature of the trials (van Staa et al, 2014).

In the Netherlands there was a similar experience. A trial based on the Integrated Primary Care Information Database found that it was possible to collect high-quality data this way. However, patient recruitment was poor because eligibility assessment took too long to be feasible in a general practice setting (Mosis et al, 2006).

Table 1: Pragmatic randomized trials in routine care with follow up in EHR/registers

Trial	Disease	No of patients or clusters	Interventions	Primary outcome	Cost outcomes	Q.o.L.	Reference
TASTE	Myocardial Infarction (MI)	7 200	Balloon dilatation of coronary arteries vs thrombus aspiration followed by coronary angioplasty	Death within 30 days	Readmission with MI and heart failure. Length of inpatient stay	No	Fröbert et al (2013)
SWEFOT	Rheumatoid Arthritis (RA)	258	Biological versus non-biological disease modifying therapy	Disease activity score	Health care costs, work loss	EQ-5D	Van Vollenhoven et al (2012), Karlsson et al (2012), Eriksson et al (2013; 2014)
SLITS	Obesity	2 508	Gastric bypass surgery with or without closure of mesenteric slots	Post-operative ileus	No	No	Not yet published

Table 1 continues on next page

Table 1 (cont.)

Trial	Disease	No of patients or clusters	Interventions	Primary outcome	Cost outcomes	Q.o.L.	Reference
RETRO	Patients with hypercholesterolemia and high cardiovascular risk	301	Simvastatin compared to atorvastatin	Major clinical outcomes ¹	No	No	Van Staa et al (2014)
eLUNG	Chronic obstructive pulmonary disease (COPD)	31	Immediate antibiotics compared to deferred or no antibiotics for exacerbations	Hospital admission for COPD exacerbation and prescribing of oral Corticosteroids ¹	Hospitalizations and other health care costs	EQ-5D	Van Staa et al (2014)
eCRT	Antibiotic use in primary care	Planning to include 50 practices per group (cluster randomization design)	Electronic decision support to reduce antibiotic prescribing	Proportion of RTI consultations with antibiotics prescribed	No	No	Gulliford et al (2011)
VA diabetes	Diabetes	Adaptive randomization will assign up to 3 000 patients	Sliding scale regular insulin compared to a weight-based regimen for control of hyperglycaemia	Hypoglycaemia, hospital stay and rates of infection and renal injury	No	No	Fiore et al (2011)
SCOT	RA patients who take NSAIDs in the long term	N.a.	Celecoxib vs traditional NSAIDs in patients with arthritis	Hospitalisation, death, cardiovascular event	No	No	McDonald et al (2013)

Table 1 continues on next page

¹ The primary objective was in fact to evaluate the feasibility of conducting point-of-care trials using routinely collected data.

Table 1 (cont.)

Trial	Disease	No of patients or clusters	Interventions	Primary outcome	Cost outcomes	Q.o.L.	Reference
MI-FREE	MI	5 855	Full coverage vs usual pharmacy benefits post-MI	Medication adherence, major cardio-vascular event	Direct medical costs	No	Choudry et al (2011)
DETOX	Acute MI	6 600	Oxygen in acute MI vs room air	All-cause mortality	Yes	No	Hofmann et al (2014)
SORT OUT V	Coronary artery lesion patients	2 468	Biolimus vs sirolimus eluting stent	Composite of efficacy and safety	No	No	Christiansen et al (2013)
REDUCE MRSA	Infections in intensive care units	74 256 (43 hospitals in cluster random-ization)	Targeted vs universal decolonization	MRSA-positive cultures	No	No	Huang et al (2013)

6 Discussion and policy implications

In summary, we can conclude that there seems to be good reasons for health care to embrace new methods to obtain evidence about the efficacy, safety and cost-effectiveness of various treatments and procedures. We have reviewed the opportunities and obstacles for one such method, pragmatic randomized trials. This leads to some policy relevant conclusions discussed below.

6.1 Not all questions can be addressed in pragmatic trials

First, we note that not every clinically relevant question can be addressed in a pragmatic trial. They will for instance complement rather than replace the regulatory trials for pharmaceuticals. The regulatory trials are explanatory with the objective to test if a new intervention can work in principle. As Schwartz and Lellouch (2009) outlined, these trials are aimed at understanding the biological effects of a new treatment. This step is fundamental and cannot be skipped, but it is different than figuring out which treatment is preferred for which patient. Pragmatic trials have their main role when there is reasonable certainty regarding the risk/benefit trade-off, but insufficient knowledge on comparative effectiveness and effectiveness in the real world clinical setting with heterogeneous populations (van Staa et al, 2014).

We have found very few examples of health economic evaluations based on pragmatic trials. This is both unfortunate and a bit surprising since the pragmatic trial lends itself well to research into the cost-effectiveness of treatments.

6.2 Evaluation plans are needed

When new treatments are introduced, there would be much to gain if there was a plan for how these will be evaluated in a systematic way. This applies to both drugs and other treatments. Treatments other than drugs do not have the same strong mechanisms for approval and reimbursement as drugs, but in principle there is the same need to assess effect and safety.

This would require a stronger link between the decision to begin using treatments and the decision of what additional knowledge is worth acquiring. There are methods developed to assess the value of additional information (for example, see Claxton et al (2004) and Meltzer et al (2011)), but they are not widely used. For drugs, reimbursement and health technology assessment authorities can change this situation by imposing requirements for initial and continued reimbursement. An important step would be to increase the requirements (or give a premium) for direct evidence from head-to-head studies. This would increase the incentives to produce knowledge more relevant to treatment effectiveness. Regulatory authorities often have requirements for additional data, but they mainly concern safety.

There is often considerable uncertainty concerning long-term effects, side effects and costs in the initial reimbursement decision. This is to some extent inevitable, since a balance must be struck between, on the one hand being reasonably sure of a new treatment's cost effectiveness, and the adverse effects of delayed access for patients on the other. But this can be managed by reconsidering the reimbursement decision some time after the launch of a new drug. Continued reimbursement, or a recommendation as first-line therapy, could be conditioned on improved evidence of a positive risk-benefit ratio or cost-effectiveness. As a result, the incentives to invest in activities that generate clinically relevant knowledge of high quality after launch would increase.

6.3 There are challenges in the supply of data

In the future, we expect data collection in pragmatic trials to be based on electronic health records to a greater extent. However, today electronic health records do not always contain the right information and there are frequently problems with data quality. Disease registers can sometimes, but far from always, be used instead. Starting new registers for research purposes is probably not feasible or rational, because registers are not the optimal solution in all disease areas. There are often technical and legal issues that have not been resolved. One problem which has been highlighted in the debate in Sweden is double reporting of data into both medical records and registers. There are many primary health care workers who do not perceive that the benefits outweigh the disadvantages of reporting to the registers.

There is great potential for increased international cooperation in this area. Much of the knowledge needed, for example concerning the relative efficacy can be developed jointly for several countries because it is not so dependent on context. It can then be adapted locally (with e.g. local unit costs) to increase relevance for policy makers in different countries.

6.4 There are challenges with research governance

Experience has shown that it is crucial to keep the trials simple for participating clinics (van Staa et al, 2014). Otherwise the clinics will not be able or willing to allocate the necessary time to the study. This is likely more of a challenge in primary care than in specialist care. This is partly a matter of creating a stronger culture of learning in health care, and potentially incentivizing such a culture. It is also a matter of experience. There probably needs to be a few successes and some examples that illustrate to clinicians that it is worthwhile to

participate (Lauer and D'Agostino, 2013). Experiences in the U.K. were encouraging in that the actual experiences of GPs to recruit patients in an unscheduled appointment were generally more positive than the hypothetical views of GPs (van Staa et al, 2014). The research governance including the approval process, obtaining consent and institutional review must be more efficient than today (Sugarman and Califf, 2014). There is also a widespread problem of funding pragmatic trials that must be addressed (Tunis et al 2003).

6.5 Better, safer and more cost-effective care

In summary, we believe that pragmatic trials using disease registers and/or electronic health records for data collection can contribute to affordable generation of knowledge regarding efficacy, safety and cost. Implementation of knowledge from such studies could in the future be important in moving towards a better, safer and more cost-effective care. Pragmatic trials could bridge the evidence gap remaining after the mandatory testing program for drugs, as well as provide high-quality data even after launch. Also, this type of study could be conducted for other interventions than drugs.

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