

# The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials

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## Scientific summary

### Evaluation of two randomised point-of-care trials

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# Scientific summary

## Background

Pragmatic trials compare the effects of different decisions in usual clinical practice. Point-of-care trials are pragmatic trials that use routinely collected electronic health records (EHRs) to simplify identification of eligible patients and collection of data for end points. Ideally, point-of-care trials should apply interventions that mimic actual clinical practice and enrol representative samples of clinicians and patients.

## Objectives

This research had the following aims:

- i. To evaluate the feasibility of point-of-care trials. Deliverables included successful completion of two pilot trials, development of a scalable information technology (IT) system for clinicians' notification during consultation and data processing, documentation of operational experiences, review of adherence to Good Clinical Practice (GCP) guidelines and analysis of fraud detection and scientific and ethical principles.
- ii. To identify the barriers and facilitators for clinicians and patients who do or do not wish to participate in point-of-care trials and to document the experiences of trial participants.
- iii. To ascertain perceptions and attitudes among primary care staff concerning the process of computerised trial recruitment (CTR) and opinions about the software used to flag potentially eligible trial participants.

## Methods

The two pilot trials were conducted in English and Scottish general practices that contributed their EHRs to a research database (including a total of 459 practices). One pilot trial (Retropro, funded by the Wellcome Trust) compared simvastatin and atorvastatin in patients with hypercholesterolaemia and a  $\geq 20\%$  10-year risk of developing cardiovascular disease. The other trial [eLung, funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment programme] compared immediate (prophylactic) with deferred or non-use of antibiotics in patients with mild to moderate exacerbation of chronic obstructive pulmonary disease (COPD). The recruitment targets were 300 and 150 respectively. Patients were recruited by general practitioners (GPs) in practices that contributed data to an EHR research database. End points of interest in Retropro included major clinical outcomes and treatment continuation over time (as recorded in the EHRs). For eLung, end points included hospital admissions recorded in EHRs and completion of the European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaires. eLung required recruitment during an unscheduled consultation with monitoring of EHR data entry and immediate flagging and GP notification (i.e. hot recruitment). Retropro also involved sending invitations to patients to attend special consultations (i.e. cold recruitment). GPs were required to complete web-based protocol and GCP training, and required governance approvals were obtained for both trials. The EHR database was used to identify potentially eligible patients; GPs had to confirm eligibility and patients were then randomised using a concealed allocation schedule. In neither trial were patients or clinicians blinded to the identity of the group to which they had been allocated. We used central data monitoring and no site visits by research staff were intended.

## Results

### *Practice recruitment*

A total of 58.8% of the practices ( $n = 270$ ) in the EHR database expressed interest in participating. A further 107 practices (23.3%) replied but declined. The number of interested practices dropped substantially with each stage of the governance process including site contracts, local approval forms, web-based GCP and protocol training (even GPs who had prescribed antibiotics or statins widely were required by research governance to complete protocol training). 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.

### *Research governance*

The overarching NHS governance review took 2 years from original application to approval, followed by local approvals (which overall took a further year in England, but only 2 months in Scotland). Several regions demanded local modifications of the trials, including localised consent forms and, because of prescribing guidelines, mandatory switching from atorvastatin to simvastatin in Retropro 3 months after trial entry. Several GPs were also warned that Retropro would adversely affect their statin performance targets (most regions restricted atorvastatin prescribing). Review by the ethics committee resulted in a considerable lengthening of the informed consent form. An independent review of compliance with GCP requirements concluded that the recent risk-adaptive approach of GCP would be well suited for point-of-care trials. However, the study team found that this approach addressed only 1 of the 10 barriers experienced by clinicians in the conduct of point-of-care trials. Governance procedures were found to have substantially affected the intended simple nature of the trials.

### *Qualitative analysis of computerised trial recruitment*

Interviews were conducted with nine GPs and four practice nurses on the process of CTR. They were generally positive about the principle of CTR (flagging during consultation). However, trials which did not include patients with acute illness were favoured. Time was perceived to be the biggest barrier to recruiting patients into the two trials. Nurses did not consider informed consent to be a barrier to recruitment, whereas most GPs felt that it would be too difficult to seek informed consent within a regular consultation.

### *Information technology system*

Dedicated software was developed for the point-of-care trials. It allowed for instantaneous monitoring of EHR activities, flagging and clinician's notification during consultation of trial eligibility, complex eligibility assessments using the EHR database, daily eligibility review, confirmation of eligibility and randomisation on the study website, daily monitoring of side effects and long-term follow-up of major clinical outcomes. It also facilitated the central 'on and off' control of recruitment and flagging at a site. The biggest challenge was the loading of the flagging software on GPs' desktops and the limited time available for testing resulting from delays in obtaining research approvals.

### *Patient recruitment and trial monitoring*

Retropro successfully completed recruitment (301 patients), whereas eLung recruited only 31 patients over a 6-month period (out of a target of 150 to be recruited over 24 months). Retropro recruited 20.6% of all statin starters in recruiting practices and 1.1% of all statin starters in the EHR database; the comparable numbers for eLung were 32.3% and 0.9% respectively. Several strategies were used for patient recruitment. Patients could be recruited either through the flagging software or through direct access to the trial website. Practices varied in their interest in using flagging for recruitment and in the preferred criteria for flagging. A challenge in Retropro recruitment was the inconsistency of risk scores in predicting cardiovascular risk resulting. A challenge in eLung was established practice in antibiotic prescribing.

We reviewed potential scenarios of fraud in point-of-care trials. The risk of inventing patients and fabricating data was considered low. The biggest risk was considered to be failure to seek adequate

informed consent. We used Mahalanobis distance to monitor for data irregularities at a site. Our analyses showed that the distribution of the Mahalanobis distance at the best recruiting Retropro site was comparable with that of other trial sites and a random sample of statin users in non-trial sites.

### *Views of clinicians on point-of-care trials*

Twenty-seven GPs participated in the interviews of their experiences, including nine GPs who declined from the outset (GP decliner) and three GPs who initially accepted participation in eLung but later withdrew (GP withdrawal). The 15 GPs who accepted eLung comprised eight GPs for whom set-up was incomplete and seven GPs who were recruiting. It was found that a lack of strong personal interest in research enables the influence of other negative pressures or barriers to result in a decision to decline participation in a study. Conversely, a strong personal interest in research appears to motivate a GP to accept participation in a study and potentially overcome those same barriers to research in primary care. Of the eight GPs who identified the need for the study to be adequately remunerated to cover study costs, only one considered this the most important factor influencing their participation decision. Opportunistic patient recruitment during a routine GP consultation was found to be the most controversial element of eLung. The over-riding concern expressed by nine GPs was a lack of time to include an additional task in the routine patient consultation. The use of computer-based pop-up alerts was an important influential factor, positively for 10 GPs and negatively for three GPs. The negative views towards computer-based pop-up alerts appear to be based on a particularly strong dislike of this method from existing use in routine care. In contrast, the GPs' positive views regarding pop-up alerts included excitement about their potential use in trials and, in particular, their time-saving attributes and efficiencies to reduce workload. The actual experiences of GPs to recruit patients in an unscheduled appointment were generally more positive than the hypothetical views of GPs. Most GPs (3/4) reported that the process took 5 minutes and was straightforward and feasible on most occasions. Twenty-six out of 27 GPs expressed their strong support for the use of EHRs to collect outcome data for point-of-care trials. Twenty-three out of 24 GPs expressed a preference for a small number of participants per site (in the region of 8–10). Nearly all GPs recommended input from GPs to inform the design of future trials and advocated the use of flexible recruitment strategies. Additional support for practices in areas with high level of deprivation was also recommended.

### *Views of patients on point-of-care trials*

Ten patients were interviewed to discuss their reasons for, and experiences of, accepting to participate in eLung. The main reason that the patients agreed to take part in eLung was in the hope it might improve their own health (6/10) or the health of other people who may suffer from COPD in the future (4/10). Seven of the 10 patients cited their excellent doctor–patient relationship as a key influencing factor in their decision-making process. All patients considered it acceptable to be recruited during the routine GP consultation despite their ill health and to use EHRs to collect trial outcome data to be acceptable. A limitation was that we were unable to interview any patients who declined to participate in eLung.

### *Scientific challenges*

As data quality is crucially important for point-of-care trials that use EHRs, we propose a four-step approach to test data quality, three of which should be conducted prior to the start of a trial. The first step could be the development of an algorithm to define the end points of interest in the EHRs. Given the heterogeneity in information in the EHRs, one approach could be to estimate the probability that a patient was correctly classified based on the information in EHRs and linked databases (i.e. positive predictive value). The validity of the algorithm used to identify the end points of interest in the EHRs could then be tested as the second step of data quality assurance. This could include the evaluation of known associations with the end points of interest. The exclusion of sites with poor EHR quality could be the third step. For example, statistical cluster analysis could identify sites with a pattern of unusual recording of the trial end points. The fourth step would be to apply this validated algorithm to the trial population. In addition, the prospective, randomised, open, blinded, end point design could be used to review recorded end points of interest in the trial.

Patients and clinicians will typically not be blinded in point-of-care trials and know which treatment the patient was randomised to. Bias in the measurement of end points is thus a risk if perspectives or opinions differ about the relative merits and disadvantages of the treatments being compared. This bias may occur particularly with patient-reported outcomes, but is likely to be less of an issue with major clinical outcomes (if diagnosis and recording are not influenced by awareness of intervention). The lack of a placebo has been considered a limitation of point-of-care trials due to, for example, differential behavioural change with the interventions being compared. Once a drug is in clinical use, however, placebo effects should be maximised to improve treatment outcomes, and so these may be important considerations for clinical decision-making, which is the focus in point-of-care trials.

### **Value of information analysis**

This analysis was conducted to establish which end points should be included in further research for eLung. A decision-analytic model was developed using literature and observational data. The total costs per patient for COPD exacerbation management for the 'antibiotics' and 'no antibiotics' arms were estimated to be £329 and £448 respectively. However, the estimated gains in quality-adjusted life-years (QALYs) were minimal with an incremental effectiveness of 0.004 QALYs per patient. The expected value of perfect information was found to far exceed the cost of a trial. It would be of most value to target future research to obtain more precise estimates of health-related quality of life.

## **Conclusions**

### **Main lessons**

Electronic health record point-of-care trials are feasible, although recruitment of clinicians is a major challenge due to the complexity in trial approvals. Trial interventions and participating clinicians and patients should be typical of usual clinical care, simple to initiate and conduct, and considered quality improvement, regulated under Good Medical Practice guidelines.

### **Recommendations for research**

- i. Develop evidence and implement risk proportionality in trial governance and conduct.
- ii. Develop strategies to address the specific challenges unique to point-of-care recruitment and to involve GPs and commissioners in identifying research priorities.
- iii. Develop consent procedures informed by preferences of patients; alternative models of consent (of content and timing) should be evaluated.
- iv. Obtain patient views on how to deal with and communicate uncertainty.
- v. Measure and acknowledge systematically uncertainty in guidelines.
- vi. Develop statistical models for the measurement of EHR data quality.
- vii. Test risk prediction and patient identification strategies in randomised trials.

### **Overall conclusion**

The real challenge is not the technical infrastructure to implement electronic point-of-care trials, but a wider appreciation that clinical research is essential to inform patient-centred clinical practice. Enabling many more clinicians to participate in trials will require considerably simplified research governance with consent that is tailored to individual needs and uses IT to communicate, including consent some time prior to randomisation. Many more clinicians and patients should be involved in controlled trials to help reduce important uncertainties of routinely used interventions. Randomisation to address uncertainty should be a matter of routine.

## Trial registration

The trials are registered as ISRCTN33113202 and ISRCTN72035428, ISRCTN Register, Current Controlled Trials.

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