Deliverable 1.3:

Final validation of the feasibility of TRANSFoRm
to deliver the GORD RCT

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**Abbreviations**

- **CROM**: Care reported outcome measures
- **eCRF**: Electronic case report form
- **eHR**: Electronic health record
- **EU**: European Union
- **EudraCT**: European drug regulatory affairs Clinical Trials
- **GCP**: Good Clinical Practice
- **GP**: General practitioner
- **GORD**: Gastro-oesophageal reflux disease
- **KI**: Karolinska Institutet
- **LA**: Los Angeles classification system of oesophagitis
- **NERD**: Non-erosive reflux disease
- **PPI**: Proton pump inhibitors
- **PROM**: Patient reported outcome measure
- **QoL**: Quality of life
- **RCT**: Randomised controlled trial
- **RDQ**: Reflux Disease Questionnaire
- **SF-12**: Short form 12
- **Sponsor**: The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
- **TRANSFoRm**: Translational Research and Patient Safety in Europe, an EU project within the 7th framework program
- **UK**: United Kingdom
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A: Validation study paper/publication (Mastellos, Blizniuk et al. 2015)

B: Evaluation protocol paper/publication (Mastellos, Andreasson, et al., 2015)

C: RCT outcome paper/manuscript (Andreasson, et al., draft)
Summary

The aim of the GORD use case was to define the functionalities needed to perform a study to answer the research question “what gives most symptom relief and the best health related quality of life, on demand or continuous use of proton pump inhibitors?”. Using the functionalities identified during the development of the use case, a set of tools were developed, GCP certified and evaluated. The evaluation was performed in two steps. First, a validation study was performed to test the feasibility to use the TRANSFoRm tools for a clinical trial in primary care. The tools were installed in three practices in Poland and were tested by 5 GPs and 10 patients that later were interviewed about their experiences working with the tools. During the validation study, GPs were satisfied with the tool for collecting clinician reported outcome measures (CROM), but stressed the importance of thorough training before use. Patients were overall content with the tool for collecting patient reported outcome measures (PROM), but expressed the concern that the level of technical knowledge might limit the use of the tool in older patients. Second, an evaluation study in the form of a meta-RCT was performed in Greece, The Netherlands, Poland and the UK with a head to head comparison between the TRANSFoRm tools and standard methods for conducting RCTs in primary care. As part of the meta-RCT, user experiences were collected by means of interviews. In the evaluation study/meta-RCT, a total of 602 patients were recruited in the study, 295 in the TRANSFoRm arm and 307 in the control arm. There was no significant difference in recruitment rate between the TRANSFoRm arm and the control arm with a large range in recruitment rate and duration between practices (43% vs 53%, p=.16). TRANSFoRm practices recruited a mean of 2.84 patients per week compared to 2.39 in the control arm (p=0.67). There was a significant difference in CROM completion rate between arms favouring the TRANSFoRm arm (85% vs 71%, p<.001). In contract, the PROM completion rate was significantly higher in the control arm (61% vs 100%, p<.001). There were no differences in the average time taken to recruit a patient between arms. Technical, cultural and implementation barriers were identified by GPs that, if improved, could further increase the effectiveness of TRANSFoRm in recruiting primary care patients in clinical trials. Having the patients fill out the PROM using the apps was found to be one of the major challenges for both GPs and patients. In conclusion, the TRANSFoRm system was proven to be as efficient as manual recruitment of patients, but also the preferred method of recruitment among GPs. The meta-RCT demonstrated that the TRANSFoRm system can be used to perform a clinical trial in primary care in several localities across Europe.
Overview

The objective of TRANSFoRm included to develop well-defined use cases to inform the development of principles, models, standards and tools to progress the Learning Health System (LHS). The GORD ‘Clinical Trial’ use case aimed to support the integration of Clinical Trial functionality into routine healthcare, including triggers and alerts, development of an electronic Case Report Form (eCRF), integrated with the electronic Health Record (eHR) for Clinician Reported Outcome Measures (CROM) collection, and capable of being triggered in real time from the eHR when eligible subjects consult, and web and mobile apps for Patient Reported Outcome Measures (PROM) collection. The full description of the GORD use case is found in deliverable D1.1. The research question of the use case is to determine the effectiveness in terms of symptom control and event-initiated assessment of quality of life in subjects with GORD randomised to either on-demand or continuous PPI.

The objective of Work task 1.5 was to test the feasibility, reliability and validity of the clinical trial support tools developed as part of the TRANSFoRm GORD use case. In this report, we present and discuss the results of this evaluation. The evaluation was done in three steps: GCP certification, usability testing and a controlled evaluation by comparison with standard methods for conducting an RCT. In this report, we present the GCP certification, the validation study results and the evaluation study results. The analysis of the outcome of the clinical research question was not included in the 1.5 work task and will be published separately.

1. Introduction

1.1. Background to the GORD use case

Gastro-oesophageal reflux disease (GORD) includes a spectrum of disorders mainly caused by the retrograde flow of acid gastric contents from the stomach into the oesophagus, causing symptoms and/or oesophageal mucosal damage. Heartburn and acid regurgitation (a bitter burning taste at the back of the mouth) are the most typical symptoms of GORD (Klauser, Schindlbeck et al. 1990; Dent, Armstrong et al. 2004; Group 2004). According to the Montreal criteria (Vakil, van Zanten et al. 2006), the spectrum of GORD goes from non-erosive reflux disease (NERD, reflux symptoms without macroscopically visible erosions), erosive esophagitis (which might be symptom free (Ronkainen, Aro et al. 2005)) of the squamous mucosa, Barrett’s esophagitis (i.e. the squamous mucosa has been replaced by goblet cells with malignant potential), and adenocarcinoma of the distal oesophagus (Lagergren 2005; Zagari, Law et al. 2010). According to the Rome (Drossman, Corraziari et al. 2006)
and Montreal (Vakil, van Zanten et al. 2006) criteria, GORD is defined separately from dyspepsia, although this dissociation is not always applied in the UK and Canada.

GORD is a common chronic but often intermittent disease (Nebel, Fornes et al. 1976; Spechler 1992; Isolauri and Laippala 1995; McDougall, Johnston et al. 1996; Agréus, Svärdsudd et al. 2001; Nocon, Keil et al. 2006). In a recent systematic review using an explicit definition of GORD (Dent, El-Serag et al. 2005), the prevalence was shown to be between 10 and 20% in Europe and North America. The notion of an increase in GORD prevalence is supported by a longitudinal study from Sweden, showing an absolute increase in GORD by 2% per decade since 1986 (Agreus 2015). The increase in GORD is thought to be due to increasing obesity (higher intra-abdominal pressure) and the lowered prevalence of Helicobacter Pylori in the stomach (Agreus 2015). The prevalence of H. Pylori is decreasing in countries with higher prosperity and so is gastric atrophy with lowered acid secretion. GORD is treated with proton pump inhibitors (PPI) (Bishop, Furman et al. 2007; Gisbert, Cooper et al. 2009), H2-blockers or antacids. About 20% will have persistent or intermittent troublesome symptoms in spite of PPI treatment (Delaney 2004).

GORD is mainly treated in primary care. Standard treatment of GORD is lowest effective dose of PPI e.g. 20 mg omeprazole per day or on demand, i.e. when the patient experiences bothersome symptoms of GORD. Data is conflicting on which of these treatment regime is superior as there are studies in favour of both on demand and continuous use of PPI (2014). If there are no differences in treatment effects, general use of on demand PPI therapy would decrease treatment costs for PPI. If however, patients receiving on demand therapy perceive more symptoms, worse quality of life and lower self-rated health, this treatment is likely to lead to a higher burden of disease. Importantly, the present study is the first pharma independent randomized controlled trial of PPI treatment regimes. In addition, this is the first inter European study including several countries: the Netherlands, Belgium, UK, Poland and Greece aiming to lead to generalizable results across Europe.

The endpoints in previous studies have been willingness to continue the allocated treatment regime and symptoms (Tsai, Chapman et al. 2004; Bour, Staub et al. 2005; Sjostedt, Befrits et al. 2005; Kusano, Hongo et al. 2012). Few studies have investigated quality of life and to date no study has investigated the difference in self-rated health between on demand and continuous PPI treatments for GORD. The present study is one of few with the power to differentiate treatment effects in terms of quality of life and self-rated health. Self-rated health is a highly relevant outcome as poor self-rated health is an independent predictor for future ill health, future morbidity (Pijls, Feskens et al. 1993; Weisen, Frishman et al. 1999; Shankar, Wang et al. 2008; Riise, Riise et al. 2014), health care consumption (DeSalvo, Fan et al. 2005; DeSalvo, Jones et al. 2009; Halford, Wallman et al. 2012), sick
leave (Halford, Wallman et al. 2012) and mortality (Idler and Benyamini 1997; DeSalvo, Fan et al. 2005; DeSalvo, Bloser et al. 2006). This is an outcome that has never been used to differentiate the treatment effects of on demand vs continuous use of PPI.

GORD is a chronic disease with a negative effect on quality of life (QoL) (Coyne, Wiklund et al. 2003; Madisch, Kulich et al. 2003; Wiklund and Talley 2003; Ronkainen, Aro et al. 2006), and as reflux symptoms are common, and for some people harmless, the disorder is defined as a disease when QoL is affected (Vakil, van Zanten et al. 2006). Thus, patient reported outcomes such as symptom frequency and severity, QoL and self-rated health are important measures (Dent, Armstrong et al. 2004) but are rarely used in primary care today. In addition, due to the diversity of patients and the structure within primary care, there are major difficulties in conducting trials within primary care. Due to logistical difficulties in conducting a trial in primary care, and despite most patients being treated in primary care, the vast majority of patient research is conducted in secondary care.

1.2. GORD use case clinical trial workflow

The use case study designed to answer the research question was a clinical trial where patients with GORD were randomized to either on demand or continuous use of PPI. Eligible patients were adults 18 to 65 years of age with GORD. After study information was communicated and informed consent collected, GPs filled out the Clinical Reported Outcome Measures (CROM) for the first visit using the TRANSFoRm eCRF tool. After the CROM were filled out, patients were randomized to the allocated treatment. After the visit, patients were instructed to fill out the Patient Reported Outcome Measures (PROM) including demographics, drug use, symptom burden, quality of life and self-rated health. After 8 weeks, patients were invited to return to the practice for collection of follow-up CROM and planning for future treatment with the GP. The patient would then fill out the follow-up PROM.

1.3. Identified functionalities of TRANSFoRm tools

A list of functionalities were identified for the execution of the GORD use case clinical trial in primary care (Andreasson, Ellenius et al. 2011), see table 1 for an extended list. Based on the work situation for many general practitioners (GPs), emphasis was put on functionalities that enable the recruitment of patients and study specific data collection to be performed during standard consultations.
### Table 1. The main functionality requirements of the use case

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<th>Tool</th>
<th>Comment</th>
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<td>Find patient</td>
<td>eCRF</td>
<td>Possible eligible patients flagged in eHR for real time recruitment</td>
</tr>
<tr>
<td>Randomize patients</td>
<td>eCRF</td>
<td>Contact with randomization agent or built in randomization tool</td>
</tr>
<tr>
<td>Data linkage in real time</td>
<td>eCRF</td>
<td>Linking research data from web based questionnaires, eHR and other databases in real time to provide a seamless view for the clinician *Current version of tool only link to eHR</td>
</tr>
<tr>
<td>Data display for clinician</td>
<td>eCRF</td>
<td>Prepopulation and presentation of semantically controlled data from a variety of sources. Flag missing or inconsistent data. *Current version of tool does not flag missing or inconsistent data</td>
</tr>
<tr>
<td>Data collection CROM</td>
<td>eCRF</td>
<td>Correction and entry of data by clinician</td>
</tr>
<tr>
<td>Data approval of clinician</td>
<td>eCRF</td>
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<td>Data collection PROM</td>
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<td>Completion of questionnaires by patient</td>
</tr>
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<td>Anonymisation of data</td>
<td>DNC</td>
<td>Removal of personal identifiers before data transfer from clinic to researcher in line with the TRANSFoRm confidentiality framework</td>
</tr>
<tr>
<td>Data storage</td>
<td>TSS</td>
<td>Data stored in a format that can be delivered and used by researcher</td>
</tr>
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<td>Monitoring</td>
<td>Monitoring workbench</td>
<td>Overview of number of filled out forms per practice and locality</td>
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Abbreviation: CROM=clinician reported outcome measures; PROM=patient reported outcome measures
1.4. GORD use case tools

In the TRANSFoRm GORD use case, tools have been developed to collect CROM and PROM data and to monitor data collection. The work tasks and corresponding deliverables for the development of these tools are presented in table 2. First, there is the eCRF tool developed as an add-on to the eHR system that is used by the clinician. In addition to collecting CROM, the eCRF tool also makes eligibility checks, takes informed consent and randomizes the patient (with the help of the study system). A similar solution has been brought forward by the US Food and Drug Agency (2014). The eCRF had several forms for the GP to complete: 1) inclusion/exclusion form, 2) consent form, 3) CROM form for visit 1 and 4) CROM form for visit 2. In the case of patients that did not want to participate, there is a study statistics form that collected the reason for declining; completing this form prevents further notification about the study. After the forms for the first visit have been completed a withdrawal form is available to the GP. This also records reason for withdrawal. Second, there is an application that can be used on smartphones and in web browsers was developed for the collection of PROM. Third, there is a monitoring workbench that allows a coordinator to monitor the progress of the inclusion of patients and the completion of CROM and PROM forms per practice and locality.

Table 2. Work tasks and corresponding deliverables for the development of the TRANSFoRm clinical trial tools

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<th>Deliverable</th>
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<td>7.2 Terminology service</td>
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<td>7.3 Metadata repository</td>
<td>Work with CDISC on using CDISC SHARE</td>
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<tr>
<td>7.4 eCRF infrastructure</td>
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<td>7.6 mobile eHealth</td>
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1.4.1. Vendor engagements

At the time of the evaluation study, five vendors were working with TRANSFoRm to develop the eCRF add-on to their eHR systems; Asseco in Poland, University of Crete in Greece, INPS and TPP in the UK, and TransHIS in the Netherlands. The add-on to be used with TPP was not ready in time to be used in the RCT on account of differences between demonstration and production versions of the TPP system, but was completed from a technical perspective.

A typical engagement with a vendor comprised an initial set of discussions during which the Learning Health System paradigm and the TRANSFoRm approach were described to obtain buy-in from the company decision makers. Two key commitments required from the vendors were access to their Application Programmer’s Interfaces (APIs) which is used to generate a clinical document for a patient’s entire electronic health record, and full information on how their data was coded. Once this was obtained, a Data Source Model (DSM) and a CDIM-DSM mapping model would be produced to enable the translation of TRANSFoRm data requests against the clinical document. Finally, the DNC forms interface would be integrated directly into the EHR system interface or agreed to be available on the computer task bar.

Discussions were also held with MicroHIS in the Netherlands and Crossuite in Belgium. However, MicroHIS had to leave the project when the project key employee left the company and Crossuite’s eHR system were not labelled for use in primary care. With MicroHIS developmental work had already began when they left the project.

1.4.2. GCP certification

In order to achieve Good Clinical Practice (GCP) certification, the TRANSFoRm system underwent a series of tests, including Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). These tests took place during the validation stage and established the functional correctness of the system, with respect to the requirements and specification, as well as the integrity of the data. The non-functional aspects examined included training materials, technical support, skill level of the development teams, and software quality assurance procedures.

The following tools underwent GCP certification:

- TRANSFoRm Study System (TSS)
- Study Database
- TSS Web application
For each of the tools, the full set of IQ, OQ and PQ documents was generated. In addition to these, a
general System Documentation, Training Plan and Developer Evaluation were produced.

1.4.2.1 Installation Qualification (IQ)

The main point of Installation Qualification (IQ) was to ensure that all the necessary verification is
performed after installation of the system. It consists of following parts:

1. Verification that all hardware is correct
2. Verification that all system components are properly installed
3. Verification that all additional software has been properly installed
4. Verification of all software inputs and outputs (this is sometimes already performed in the
   form of unit testing)
5. Verification that software version numbers are correct
6. Verification that software configuration is correct
7. Verification that all source code has been reviewed
8. Verification that a backup of the software is available
9. Verification that design specifications are available and approved
10. Verification that SOPs for application operation, maintenance, backup and recovery are
    available and approved

Verification means that installation data (log), tests, drawings, requirements, etc. are available and
were checked.

The main function of the IQ is to verify and document that the system has been properly installed.
Therefore, the IQ is performed prior to executing the OQ.

1.4.2.2 Operational Qualification (OQ)

The Operational Qualification (OQ) documentation included:
1. **Acceptance of Successful Completion**: a page that requires signatures from both the patient and the developer, acknowledging that all steps within this guide have been completed satisfactorily and thus that OQ was completed positively.

2. **Installation**: information about the environment in which the software has been installed for the test.

3. **Tester**: the person conducting the test scripts, which shouldn’t be a developer.

4. **Procedures**: how to use the test scripts for the qualification and how to deal with deviations.

5. **Scripts**: lists the requirements/functions formulated as instructions; including a signature area for the tester.

6. **Completion**: the final step after the test scripts have been executed for testing. In the last step the “Acceptance Form for Successful Completion” is filled out.

### 1.4.2.3 Performance Qualification (PQ)

The PQ document complements the OQ document by adding the User Acceptance Specifications as well as regulatory requirements, for example GCP requirements, to the validation procedure. The provided requirements served as scripts to qualify the TRANSFoRm Study System. The PQ was completed together with the validation study, by a user representative in the usual clinical site environment. The successful completion of PQ verified that the TRANSFoRm Study System and its associated components are compliant with UAS, user requirements and regulatory requirements and perform well in an operative environment.

### 2. Evaluation of TRANSFoRm clinical trial tools

The goal of the TRANSFoRm GORD use case was to support the development of tools to facilitate the conduct of clinical trials in primary care, including the collection of both clinician reported outcome measures (CROM) and patient reported outcome measures (PROM). The initial aim of the use case was not to deliver a full RCT to test the clinical research question but to demonstrate the ability of TRANSFoRm to run a RCT and to deliver a proposal for full implementation/funding of the definitive study. After careful consideration we found that there was an ethical contradiction in running an RCT that is not fully powered for the research question just to evaluate the TRANSFoRm tools and so the aim with the GORD use case changed to deliver a fully powered RCT that would answer the research...
question of what gives the best symptom relief and the best quality of life, on demand or continuous use of PPI, while also evaluating the TRANSFoRm tools.

The evaluation of the tools has been performed in a two-step process. First, in the validation study, the usability of the tools was tested in practices with GPs and patients. Although the validation study was only performed in Poland, testing was performed in all localities before the start of the evaluation study. Second, in the evaluation study, the tools were tested against standard methods for performing a randomized controlled trial. The evaluation plan has been described in detail and published, see Appendix B (Mastellos, Andreasson et al. 2015).

2.1. Validation study

2.1.1. Description

The validation study was a mixed methods feasibility study to test the clinical trial tools in primary care by installing the software on the GP’s computer and letting the GP use it during consultations with real patients that were asked to participate in the study as pilot subjects. The validation study examined GP and patient acceptability of the TRANSFoRm tools.

The methods and results of the validation study have been described in detail (Mastellos, Blizniuk et al. 2015), see Appendix A.

2.1.2. Aim

To test the feasibility of TRANSFoRm tools to conduct clinical trial recruitment, data collection and follow-up in a primary care setting.

2.1.3. Prerequisites

Before the validation study could be performed, the study protocol had to be approved by the appropriate ethical review boards and the tools had to be GCP certified.

2.1.4. Ethics

Ethical review of the validation study was performed in The Netherlands by the Medical Ethical Committee of VU University Medical Center Amsterdam, with the verdict that the type of study did not require further ethical approval. As the Dutch vendor involved in TRANSFoRm at that time had to withdraw from the project, the validation study was performed in Poland instead. The validation of
the tools was included in the ethical application for the RCT in Poland and thus covered by the approval for the evaluation study in Poland from the Bioethics Committee of the Lower Silesian Chamber of Physicians in Wroclaw.

2.1.5. Methods

2.1.5.1. Participants

The study took place in Poland in May 2015. Participants were GPs and patients with GORD from three GP practices in three cities (Mielec, Piotrków Trybunalski, and Łódź). To be eligible for participation, GP practices had to i) use an mMedica EHR system delivered by ASSECO Poland S.A. – a big vendor of EHR systems in Poland –, ii) nominate one or more GPs to participate, iii) be willing and able to identify suitable study participants, and iv) provide informed consent to participate. Patients were eligible to participate if they were i) 18-65 years old, ii) had a GORD diagnosis and/or PPI prescription within the last 12 months, iii) were willing to complete PROM in electronic format, and iv) provided written informed consent to take part. A total of 5 GPs at 3 general practices and 10 patients participated in the study.

2.1.5.2. Procedure

The intervention was delivered in a controlled, real-life setting. GPs used the TRANSFoRm eCRF tool to recruit eligible GORD patients and collect baseline data. GORD patients, aged 18-65 years old, visited their GP and went through the recruitment steps described in the GORD study workflow (Figure 1). Once recruited, patients were invited by email to use the mobile or web app to fill out and submit PROM data. (e.g. quality of life questionnaire). Prior to intervention delivery, face-to-face training was provided to all GP participants by qualified study personnel. GPs were trained on how to use the TRANSFoRm system to carry out patient recruitment and baseline data collection by TRANSFoRm staff from CSIOZ. Patients did not receive any training on how to use the web/mobile app to complete and submit PROM because the app is developed to be intuitive to use to avoid the need for training of patients that may not be feasible in a full range trial.
Mimicking a standard consultation, the GP used the TRANSFoRm tool to follow the entire recruitment process including the collection of CROM. After the consultation, the patients filled out the PROM.

Following system testing and recording of CROM/PROM data, semi-structured interviews with GPs and study participants were conducted to capture in-depth information about the usefulness, ease of use and overall experience with the TRANSFoRm tools. Each interview lasted for approximately 30 minutes. As the participants did not accept voice recording for cultural reasons, all interviews were recorded using paper and pen, transcribed verbatim and translated into English by qualified bilingual personnel.

2.1.5.3. Data analysis

Interview data were analysed thematically in English using the Ritchie and Spencer’s Framework Approach. This included a series of well-established steps to ensure consistency, credibility and
traceability of findings. In particular, the analysis involved i) familiarisation with the data, ii) identification of a thematic framework based on a priori, emergent and analytical themes by which the data can be examined, referenced and indexed, iii) indexing of transcripts, iv) data charting according to specific thematic categories, and v) interpretation of the whole dataset by looking for associations among themes and providing explanations for the findings.

2.1.6. Results

Between December 2013 and April 2014, scientific personnel from ASSECO Poland S.A. invited all mMedica general practices in Poland (n=9420) to participate in the TRANSFoRm cluster RCT. Invitations took the form of pop-up messages on mMedica systems and invitation letters to the practices that expressed interest in participating in the trial. A total of 58 practices responded positively. However, only 22 practices had a mMedica licence with a cabinet module installed, which is a prerequisite for the implementation of TRANSFoRm, and therefore were considered for inclusion. A total of ten practices, which best fulfilled the trial’s practice eligibility criteria, were selected to participate in the trial. Of these ten practices, three were invited to take part in the validation study with a total of five physicians and ten GORD patients. Mielec participated with two GPs and five patients; Piotrków Trybunalski with one GP and three patients; and Łódź with two GPs and two patients. The GP group consisted of two male and three female practitioners with a mean age of 49 years. The patient group had a mean age of 48 years and included six male and four female participants. No further demographic and socio-economic data were collected for the purpose of this study.

2.1.6.1 Practitioner experience

Overall, GP experience with the TRANSFoRm eCRF tool was very positive. Respondents highlighted the role of training in increasing confidence and self-efficacy with the system and identified a number of advantages compared with standard practice.

Specifically, GPs felt that the system requires some skill to use. The training provided by a qualified member from ASSECO Poland S.A. lasted for approximately an hour. All GPs said that the training was satisfactory and equipped them with the necessary skills to perform patient recruitment.

In addition, GPs found TRANSFoRm simple and easy to use. Particularly, they said that identification of potentially eligible patients was quick and easy; randomisation and allocation of study participants simple; data collection easy; and data reporting simple. Respondents felt that TRANSFoRm could enable them to recruit patients in an easier and faster way compared with standard practice.
Respondents were generally happy with system interface. However, they also said that it would be nice to be able to view all patient forms after the end of the visit, especially the form with the randomisation result to be able to confirm each individual randomisation, as per the study protocol. All study forms were automatically stored into the Study System and local EHR system. However, with mMedica EHR specifically no client interface mechanisms were enabled to permit these forms to be viewed.

2.1.6.2. Patient experience

Participating patients expressed a positive opinion about the usability of the TRANSFoRm web/mobile apps. Overall, participants felt that the apps were simple to use, but they were concerned about the length of the questionnaires and the repetitive nature of questions that could result in patients withdrawing from the study. They also recommended giving certain patient groups, such as the elderly, the option to fill out the PROM using paper and pen, as these patients may be less familiar with new technology.

Participants felt confident to use the TRANSFoRm apps without any formal training. They found the apps simple and easy to use, but they also mentioned that some medical terms and abbreviations on the questionnaires were incomprehensible and it would be better to include some explanation of their meaning for patients to understand what they fill out. They were also concerned about the length of the questionnaires as some were found too long. Another point of concern was that some questions were repetitive and were asked twice, at their baseline visit to the GP and at follow-up. However, one participant who had participated in many studies and was accustomed to such surveys said that "the survey was done professionally and aesthetically. It took 14 minutes to complete the PROM. There was no problem with the number of questions". Despite complaining about the length of the questionnaires, users agreed that they were able to complete their PROM in a timely manner.

Participants were also concerned about the use of email to invite participants to fill out the PROM electronically. Three participants were unable to fill out their questionnaires as the email with the link to complete the PROM was landed in their spam folder, while one participant received the email but failed to open the link.

Finally, participants expressed mixed views regarding the usefulness of the TRANSFoRm apps. Half of the participating patients said that, if they had one option, they would use the TRANSFoRm apps to fill out their PROM; one did not show any preference; and the rest would rather use paper and pen. Age was identified as a limiting factor to using the ePROM apps. Participants thought that elderly patients might find it difficult to fill out their PROM electronically due to their limited exposure to
smartphone and web technologies and suggested giving them the option to use paper-based questionnaires.

2.1.7. Comments

This study provides evidence on practitioner and patient acceptability of using the TRANSFoRm clinical trial tools to conduct recruitment and follow-up in primary care. The findings show that GPs were thoroughly satisfied with the eCRF tool as it enabled them to identify, recruit and follow-up participants efficiently, potentially saving them time and effort compared with paper-based or mixed methods of recruitment. Patients also had a positive experience with the TRANSFoRm web or mobile apps for reporting PROM data. Despite some concerns regarding the self-reported questionnaires, the content and length of which are independent of whether participants use paper and pen or an app, patients found the apps easy to use. However, the results also suggest that study participants, especially those with limited exposure to smartphones and/or the Internet, should be given clear instructions on how to access and use the apps online and the option to fill out their questionnaires using paper and pen.

2.2. Evaluation study

2.2.1. Description

The evaluation of the tools was performed as a randomized controlled trial testing the clinical research question used in the GORD use case where the practices were randomized to use either standard methods for data collection or the TRANSFoRm tools. Thus, the evaluation study was a nested cluster randomisation of site for the methodological question within an individual randomised RCT for the clinical question. The protocol for the evaluation study has been published (Mastellos, Andreasson et al. 2015). The RCT for the clinical research question is a registered clinical trial (EudraCT trial number 2014-001314-25) and is presented in Appendix C.

2.2.2. Aim

The aim of the study was to compare the TRANSFoRm tools to standard methods for opportunistic clinical trial recruitment in primary care. The primary outcome of the study was recruitment rate hypothesizing that the TRANSFoRm arm will have a recruitment rate of 35% compared to 20 % in the control arm. Second, drop-out rate and data completeness were compared between arms. Third, the experiences of using the TRANSFoRm system of participating GPs and patients in the TRANSFoRm arm were investigated.
2.2.3. Prerequisites

Prerequisites for the evaluation study were that all tools were GCP certified, TRANSFoRm tools tested (i.e. validation study), contracts with the practices were in place, and ethical approval had been granted in all localities.

2.2.4. Ethical approval

Ethical approval for the RCT was sought and received in all localities before any practice was enrolled in the study. The process of receiving ethical approval illustrates the differences in application process and main concerns between the different countries.

2.2.4.1. The Netherlands

The ethical application was submitted to the Medical Ethical Committee of VU University Medical Center Amsterdam, the cost for review was EUR 3500. There were two rounds of revisions. The board asked for additional information on what practices were to be involved in the study as this information had to be included in the application, which is in stark contrast to the UK where no practice may be approached before ethical approval has been granted. Their main concern was the need for the research as it was considered obvious that the participants in the on demand group would have the best quality of life based on the type of prescription. The full review process from submission to approval took eight months. The application was submitted in English. Exception from the need for indemnity was sought with the argument that two standard treatments for GORD were used and that the patient would have received either of them as part of standard health care and the study would add no extra risk for the patient. The Dutch ethical approval demands a physician that is independent of the study that can answer any questions from potential participants regarding the study. This role was filled by ESPCG member Professor Jean Muris at Maastricht University.

2.2.4.2. Belgium

As we were working with a vendor in Belgium at the time for ethical applications, ethical approval was sought and received also in Belgium. Only a few modifications were needed to be able to use the Dutch application submitted in the Netherlands, with CROM, PROM and patient information, as the vendor was active in the Flemish part of Belgium. There were questions about indemnity from the ethics review board but this matter was resolved by a statement from the University of Antwerp that the nature of the study, where patients received either of the two approved treatments that they would have received anyway, and that any adverse events should be handled as part of standard
health care. As both University of Antwerp and Karolinska Institutet were partners in the TRANSFoRm project there was no need for a contract between the partners in addition to the roles defined in the ethical application.

2.2.4.3. Poland

The ethical application in Poland was submitted to Bioethics Committee of the Lower Silesian Chamber of Physicians in Wroclaw. The cost for review is based on the number of practices. With 10 practices involved in Poland, the total cost added up to EUR 890. The full review process form submission to approval took two months. The application was submitted in Polish and a professional translator was used to translate the protocol from English to Polish.

2.2.4.4. Greece

The ethical application in Greece was submitted to the ethical board of the University of Crete. The cost for review was EUR 500. The full review process from submission to approval took seven months and a further three months before there was an official signed document that the study was approved. The application was submitted in Greek and a professional translator was used to translate the protocol from English to Greek. In addition to the study protocol, the ethics board requested a budget for their information only. There were no difficulties during this process apart from the time delay before review and after approval until the formal document of approval was received.

2.2.4.5. United Kingdom

In the UK, the process was performed in two steps. The overall time from initial submission to final approval was six months and the cost EUR 335. First, an approval from the National Research Ethics Service (NRES) was required. The second step involved approval from NHS Research Governance, including site-specific approvals. Both steps are undertaken via the on-line Integrated Research Assessment Service (IRAS) and required an electronic signature from the chief investigator and head of department at the department of Neurobiology, Care Sciences and Society at Karolinska Institutet. The XML-file produced during the EudraCT registration process could be used and imported into the system to reduce the need for double entry which was handy. The role of principal investigator had to be swapped from Dr Anna Andreasson to Professor Lars Agréus as the chief investigator for the UK application had to be either a licensed physician, a licensed nurse or a licensed pharmacist although it is not mandatory that the chief investigator has a doctorate degree which is mandatory in the other countries.
We had an interview with the ethical committee. They wanted clarification of the study budget and the role of Karolinska Institutet as sponsor of the study. It is mandatory to include an indemnity statement for ethical applications in the UK, from which we had to ask for an exemption. Swedish law covers indemnity and Karolinska Institutet as a governmental institution at a Swedish university is bound to follow Swedish law and has no such document. Retrieving a legal document stating this in English was found exceedingly hard to produce and the ethics board granted an exemption.

Practices received reimbursement of research costs of EUR 20 per recruited patient. As it is not allowed to pay patients for participating in clinical research in the UK, patients were not paid for participation in any locality to keep incentives for participation identical across all sites. In the UK, participating practices were also compensated by the local clinical research network (£305.44 initial set up cost, £4.80 per patient approached + £40 for each patient actually recruited) for the excess service costs of recruitment and training for the study.

2.2.5. Methods

2.2.5.1. Participating practices

Practices using the eHR system were approached and asked to participate. Eight to ten practices per vendor were included in the study, and altogether 36 practices participated in the study: 8 in Greece, 10 in Poland, 8 in the Netherlands and 10 in UK. As the system for one vendor in the UK was not ready for evaluation during the time the meta-RCT was running, the corresponding 10 practices did not participate in the study.

2.2.5.2. Procedure

The included practices were paired for each respective locality based on 1. List size, 2. Number of GPs at the practice and 3. Number of PPI prescriptions per week and the practices within each pair were randomized to either the TRANSFoRm arm or the Control arm, respectively. A comparison between the two arms is given in table 3.

TRANSFoRm arm

The practices in the TRANSFoRm arm had the TRANSFoRm software installed in the practice and were trained in using the software by TRANSFoRm staff.

Control arm

The system used in the control arm consisted of an electronic case report form with built in randomization algorithm identical to that used in the TRANSFoRm eCRF tool. Although the control
arm CRF is electronic with built in randomization it had no contact with the eHR system and were lacking the functionalities of supporting patient recruitment by flagging eligible patients, prepopulating of available data and saving study data in the eHR. The control arm was also not directly based on the CDISC ODM standard. Patients completed the PROM on paper and the questionnaire was sent to the local study coordinator for data entry. The alternative approach would have been to use a commercial Electronic Remote Data Capture System in the control arm. These systems are not widely used in practice-based studies as in these so-called ‘pragmatic’ trials, usual healthcare staff use the system rather than trained researchers. UK Primary Care researchers have wide experience of using specifically-designed ‘bespoke’ web-based data collection systems as the current ‘best practice’, and we had access to these via the study co-ordinator.

Table 3. Comparison of functionalities between the TRANSFoRm and control arm.

<table>
<thead>
<tr>
<th></th>
<th>TRANSFoRm</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruitment</strong></td>
<td>Flagging patient in eHR</td>
<td>Manual identification of eligible patients</td>
</tr>
<tr>
<td><em>(consecutive)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Informed consent</strong></td>
<td>Signed paper</td>
<td>Signed paper</td>
</tr>
<tr>
<td><strong>Randomisation</strong></td>
<td>Automatic in eCRF</td>
<td>Automatic in eCRF</td>
</tr>
<tr>
<td><strong>Data Elements</strong></td>
<td>Standardised via CDISC ODM and CDIM</td>
<td>No standardisation</td>
</tr>
<tr>
<td><strong>CROM collection</strong></td>
<td>eCRF integrated with eHR</td>
<td>Web based eCRF with no pre-population</td>
</tr>
<tr>
<td></td>
<td>Prepopulated with eHR data via search linked to DNC</td>
<td></td>
</tr>
<tr>
<td><strong>PROM collection</strong></td>
<td>Web/Smart Phone also based on an ODM xml document</td>
<td>Printed questionnaires distributed by practices, prepaid envelopes provided. Data entered manually into database</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Reporting workbench</td>
<td>Manual¹</td>
</tr>
<tr>
<td><strong>Data saved</strong></td>
<td>Recoverable from EHR via DNC application</td>
<td>Not saved to HER</td>
</tr>
<tr>
<td><strong>Provenance</strong></td>
<td>Traced via system</td>
<td>Not traced</td>
</tr>
</tbody>
</table>
To reduce the workload of the country coordinators monitoring the recruitment progress, a monitoring system with counts for recruited and completed patients was developed also for the control arm web based eCRF.

Abbreviations: eHR=electronic health record, eCRF=electronic case report form, CDISC=clinical data interchange standards consortium, ODM=operational data model, CDIM, DNC=data node connector

2.2.5.3. Statistics

Differences in recruitment rate between the TRANSFoRm arm and the control arm were calculated using Wilcoxon matched-pairs signed-ranks test and the pairing from the randomization of the practices to the TRANSFoRm vs the control arm was used. Differences in completion rate was analysed using two sample test of proportions.

2.2.5.4. User experiences

GP and patient experience with the TRANSFoRm tools was assessed in follow-up semi-structured interviews in a subset of participating GPs and patients in the TRANSFoRm arm. The interviews aimed at assisting interpretation of quantitative data generated by the main evaluation study by exploring:

1. methods of recruitment and follow-up;
2. reasons for any observed variations in recruitment performances across sites;
3. barriers and facilitators to successful recruitment; and
4. areas for improvements.

2.2.5.5 Technology acceptance

We were planning to measure user acceptance of the TRANSFoRm tools using a centrally-coordinated TAM (Technology Acceptance Model) survey. TAM is a validated instrument for collecting post-hoc perceptions of a technology artefact segregated into two major domains: usefulness and ease of use. An extended TAM version was used to also capture attitudes towards use and intention to use. Due to the limited number of GPs and the fact that most GPs participated in the user experience interviews, it was decided to collect data from study participants only. Data was collected online through an electronically distributed questionnaire (See Appendix C) to all intervention arm participants and were analysed using descriptive statistics.
2.2.5.6. Economic evaluation

An economic evaluation was planned to estimate the cost of recruitment and follow-up per patient, as well as the average length of recruitment per patient. However, country-specific limitations hindered collection of adequate data for a full economic analysis. In the Netherlands, a proactive recruitment approach was adopted which did not allow to estimate the total time of recruitment (patients were identified prior to the consultation). In the UK, GPs did not complete the recruitment process to enable estimates of the time spent on recruitment and follow-up (in fact, five patients were recruited and of these only one had complete CROM and PROM data). In Greece and Poland, the eHR systems did not support accurate collection of appointment length data to estimate the average length of recruitment. The above limitations did not allow to assess the economic benefits of the system compared to control. However, to assist interpretation of the overall effectiveness of TRANSFoRm, information on the length of recruitment was collected during the semi-structured interviews with GPs from the TRANSFoRm arm and is reported in section 2.2.6.4.

2.2.6. Results

2.2.6.1. Recruitment rate

The number of recruited patients in the TRANSFoRm and control arm in all four localities and in total is presented in table 4. The total number of recruited patients exceeded 600 and was very similar between the TRANSFoRm and the control arm. Greece and Poland stood for the vast majority (96%) of all recruitments.
Table 4. Number of recruited patients per locality and arm

<table>
<thead>
<tr>
<th>Locality</th>
<th>TRANSFoRm arm</th>
<th>Control arm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>122</td>
<td>121</td>
<td>245</td>
</tr>
<tr>
<td>Netherlands</td>
<td>10</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Poland</td>
<td>156</td>
<td>177</td>
<td>333</td>
</tr>
<tr>
<td>UK</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>293</strong></td>
<td><strong>307</strong></td>
<td><strong>600</strong></td>
</tr>
</tbody>
</table>

As The Netherlands used a different method of approaching patients and the number of recruited patients in UK was very low, Greece and Poland were used to compare recruitment rates between the TRANSFoRm arm and the control arm. Detailed statistics of the recruitments for the comparison between the TRANSFoRm arm and the control arm in Greece and Poland are presented in table 5. Eight pairs of practices were available for analysis. The total number of patients recruited was very similar between the arms. The total number of eligible patients was higher in the TRANSFoRm arm, as there was one practice that had a very long recruitment time and consequently a high number of eligible patients according to the eHR. It was hypothesized that the TRANSFoRm tool would increase the recruitment rate from 20% to 35%. The average recruitment rate was 43% in the TRANSFoRm arm and 53% in the control arm with a large range in recruitment rate between practices. There was no significant difference in recruitment rate between the TRANSFoRm arm and the control arm (p=.16). There was no statistically significant difference in number of recruited patients per week between the two arms (mean TRANSFoRm=2.84 recruited patients per week vs mean control 2.39 recruited patients per week, p=0.67).
<table>
<thead>
<tr>
<th>Pair</th>
<th>Practice ID</th>
<th>Recruitment period (weeks)</th>
<th>First patient in</th>
<th>Last patient in</th>
<th>Recruited patients (N)/Eligible patients (N)</th>
<th>Recruitment rate (%)</th>
<th>Recruited patients per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PL5012077</td>
<td>24</td>
<td>2015/05/20</td>
<td>2015/10/29</td>
<td>23/184</td>
<td>13</td>
<td>0.96</td>
</tr>
<tr>
<td>2</td>
<td>PL5011633</td>
<td>22</td>
<td>2015/05/20</td>
<td>2015/10/16</td>
<td>42/401</td>
<td>11</td>
<td>1.91</td>
</tr>
<tr>
<td>3</td>
<td>PL27090450</td>
<td>19</td>
<td>2015/05/20</td>
<td>2015/09/28</td>
<td>11/56</td>
<td>20</td>
<td>0.58</td>
</tr>
<tr>
<td>4</td>
<td>PL18022089</td>
<td>28</td>
<td>2015/05/14</td>
<td>2015/11/25</td>
<td>80/82</td>
<td>98</td>
<td>2.86</td>
</tr>
<tr>
<td>5*</td>
<td>PL54711380</td>
<td>NA</td>
<td>2015/09/02</td>
<td>Dropped out</td>
<td>1 (not included in total)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>GRHIS04</td>
<td>8</td>
<td>2015/10/15</td>
<td>2015/12/04</td>
<td>21/38</td>
<td>55</td>
<td>2.63</td>
</tr>
<tr>
<td>7</td>
<td>GRHIS06</td>
<td>10</td>
<td>2015/10/05</td>
<td>2015/12/11</td>
<td>16/20</td>
<td>80</td>
<td>1.60</td>
</tr>
<tr>
<td>8</td>
<td>GRHIS08</td>
<td>7</td>
<td>2015/10/05</td>
<td>2015/11/16</td>
<td>43/47</td>
<td>91</td>
<td>6.14</td>
</tr>
<tr>
<td>9</td>
<td>GRHIS05</td>
<td>7</td>
<td>2015/10/05</td>
<td>2015/11/17</td>
<td>42/72</td>
<td>58</td>
<td>6.00</td>
</tr>
<tr>
<td>1</td>
<td>PL27092235</td>
<td>4</td>
<td>2015/05/22</td>
<td>2015/06/18</td>
<td>10/86</td>
<td>12</td>
<td>2.50</td>
</tr>
<tr>
<td>2</td>
<td>PL05010222</td>
<td>28</td>
<td>2015/05/19</td>
<td>2015/11/24</td>
<td>30/58</td>
<td>52</td>
<td>1.07</td>
</tr>
<tr>
<td>3</td>
<td>PL12021867</td>
<td>29</td>
<td>2015/05/13</td>
<td>2015/11/30</td>
<td>65/182</td>
<td>36</td>
<td>2.24</td>
</tr>
<tr>
<td>4</td>
<td>PL12020831</td>
<td>4</td>
<td>2015/09/02</td>
<td>2015/09/27</td>
<td>18/20</td>
<td>90</td>
<td>4.50</td>
</tr>
<tr>
<td>5*</td>
<td>PL27090735</td>
<td>28</td>
<td>2015/05/20</td>
<td>2015/11/27</td>
<td>54/110</td>
<td>49</td>
<td>1.93</td>
</tr>
<tr>
<td>6</td>
<td>GRHIS01</td>
<td>21</td>
<td>2015/07/03</td>
<td>2015/11/23</td>
<td>40/52</td>
<td>77</td>
<td>1.90</td>
</tr>
<tr>
<td>7</td>
<td>GRHIS02</td>
<td>23</td>
<td>2015/05/25</td>
<td>2015/10/28</td>
<td>20/30</td>
<td>67</td>
<td>0.87</td>
</tr>
<tr>
<td>8</td>
<td>GRHIS03</td>
<td>20</td>
<td>2015/07/16</td>
<td>2015/11/28</td>
<td>41/55</td>
<td>75</td>
<td>2.05</td>
</tr>
<tr>
<td>9</td>
<td>GRHIS07</td>
<td>5</td>
<td>2015/06/08</td>
<td>2015/07/10</td>
<td>20/32</td>
<td>63</td>
<td>4.00</td>
</tr>
</tbody>
</table>

*Not included in statistical analysis.
2.2.6.2. Completion rate

<table>
<thead>
<tr>
<th></th>
<th>Transform arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Completion rate</td>
</tr>
<tr>
<td>Recruited participants¹</td>
<td>293</td>
<td>Ref</td>
</tr>
<tr>
<td>CROM 2</td>
<td>250</td>
<td>85 %</td>
</tr>
<tr>
<td>PROM 1</td>
<td>251</td>
<td>Ref</td>
</tr>
<tr>
<td>PROM 2</td>
<td>171</td>
<td>61 %</td>
</tr>
</tbody>
</table>

¹ There were first visit CROM for all included participants.

All localities were included in the comparison of completion rate in the TRANSFoRm arm compared to the control arm. In the TRANSFoRm arm, 85% of those with a CROM 1 had a filled CROM 2, while in the control arm this was true for 71% (p<.001). In the TRANSFoRm arm, 61% of patients with a PROM 1 had also filled out PROM 2, as compared to 100% in the control arm (p<.001). Hence, the TRANSFoRm tool supported CROM data collection significantly better while the manual distribution of questionnaires was superior to the use of the mobile/web app for PROM data collection.

The data collected for the drop-out rates were found not reliable why we do not include an analysis of drop-out in this report, but report completion rates only.

2.2.6.3. User experiences

Participant demographics and country specificities

Demographics

Semi-structured interviews were held between November 2015 and January 2016 with twelve GPs and seven patients from the TRANSFoRm arm. Of the twelve GPs who participated in the follow-up interviews, six were from practices (n=4) in Poland, four from practices (n=4) in Greece, one from a practice in the UK and one from a practice in The Netherlands. Seven patients from five practices in Poland participated in the study. The GP group had a mean age of 49 years (median=47) and consisted of eight male and four female practitioners. The patient group had a mean age of 49 years (median=50) and included three male and four female participants. The findings from the interviews are organised by participant group and thematic category from the interview schedule.
The Netherlands

In The Netherlands, a proactive recruitment method was used because the TRANSFoRm system did not support automated patient identification. The GP (in collaboration with a research assistant from NIVEL) created eligibility lists after running a search on the eHR system to identify eligible patients. Following initial screening, the GP sent a letter to the identified patients inviting them to participate in the study. Those interested in taking part were required to fill out a form and return it to the practice. They were then contacted to attend the first visit.

United Kingdom

In the UK, there were some technical issues in the installation of the pop-up eligibility alert which delayed the recruitment process. In addition, the system did not notify GPs about missing data. Once the pop-up alert was working, GP recruited five patients and collected CROM data for three patients. The GP who participated in the interview recruited two patients but did not collect any CROM data.

Greece

In Greece, the system prevented uninsured patients or patients that used PPI over the counter to be included in the study, although these factors were not related to the eligibility criteria of the study. In addition, the system did not constrain the order of the forms, but this was corrected during the study. One practice contacted participants by phone to remind them to complete their PROM. Patients who found it difficult to use the TRANSFoRm apps completed their PROM during visit 2.

Poland

In Poland, there were intra-practice variations in the follow-up of patients. Specifically, two practices called patients to check whether they have completed their PROM using the TRANSFoRm app. Those who had not were given the option to complete them at their GP clinic during visit 2.

Practitioner experience

Recruitment process

With the exception of the practice in The Netherlands, where a proactive recruitment method was adopted, patients were recruited by the GP during the consultation using an opportunistic approach. Initial eligibility was determined by the GP after consulting the patient’s electronic health record and the pop-up window generated by TRANSFoRm. Final eligibility was determined by the GP after completing the study eligibility eCRFs with the patient and was verified by the system. After
explaining the study, GPs asked patients to read and sign a consent form. Baseline CROM data was collected by the GP during the first visit using the TRANSFoRm eCRF tool. Some information was auto-populated from the patient’s record (i.e. age, gender, medication, BMI). In case of missing data, a pop-up window would appear prompting the GP to complete all required fields (form validation was not available in the UK). Following data collection, patients were randomised by TRANSFoRm to continuous or on-demand PPI.

Follow-up process

Follow-up CROM data was collected at the follow-up visit to the clinic. PROM data was collected remotely using the web or mobile apps. Initial instructions on how to report PROM data using the apps were given to participants by their GP during the initial visit. Participants received an email notification to complete their PROM. Two clinics in Poland and one in Greece checked whether patients had completed their PROM via phone and invited those with incomplete data to fill out their PROM at the clinic during the follow-up visit.

Strengths and weaknesses of TRANSFoRm GP tools

GPs demonstrated a preference toward the TRANSFoRm system compared with existing recruitment methods. They found the system useful, easy to use and time-efficient. They were particularly happy with the patient eligibility pop-up alert, the automated randomisation function, the availability of data at any time and the system’s ability to organise the study in a more structured way while ensuring data validation (apart from the UK) and completeness. However, they also pointed out the need for well coded data for the pre-population of eCRF fields for TRANSFoRm to perform optimally, otherwise the record needs to be searched manually as with any CRF form, resulting in TRANSFoRm performing similarly to existing systems. GPs identified as a major drawback the system’s dependency on internet connection which occasionally delayed patient recruitment. When there was no network connectivity, GPs had to use another computer with internet connection to fill out the electronic forms.

Strengths and weaknesses of TRANSFoRm patient tools

GPs felt that the apps enable remote follow-up providing patients with the flexibility to complete their PROM at their own pace and place. They also felt that the apps eliminate the need for paper and enable direct data entry into the system. However, overall GPs believed that the TRANSFoRm apps are as useful and acceptable as paper-based methods for patient follow-up.
Barriers to effective recruitment

In Greece, technical issues hindered patient recruitment in the TRANSFoRm arm. The system did not allow GPs to recruit uninsured patients or patients that used PPI over the counter, although they were eligible as per the study’s eligibility criteria. Patients with the above characteristics were included in the control arm, but were excluded in the TRANSFoRm arm. The flow in the design of the system in Greece posed a significant barrier to the recruitment of study participants in the TRANSFoRm arm.

Another barrier was the limited time to recruit a patient. in the UK, GPs were required to discuss the clinical problem with the patient and recruit them into the study within the 10-minute consultation window. As a result, GPs did not have the time to go through all the recruitment steps (e.g. collect baseline CROM data), which may explain the low recruitment numbers in the UK.

An additional barrier in the UK was the big time lag between training and implementation due to difficulties with the supplier installing the software on the GP system, resulting in GPs forgetting much of the initial training. For example, a GP admitted that by the time of the study they had forgotten that patients need to fill out a written consent form and thought that this was recorded electronically on TRANSFoRm. The time lag between training and recruitment may have demotivated GPs from recruiting patients resulting in low recruitment rates in the UK.

Recruitment was also affected by cultural differences across localities. Culture consists of shared beliefs, values and attitudes among members of a particular group or society. GPs in the UK and The Netherlands said that patients were not willing to go from continuous to on-demand PPI as per the study protocol due to the belief that this would not be beneficial for their treatment, while in Poland and Greece people were less concerned about changing their medication regime.

Barriers to effective follow-up

Age and education level were identified as significant determinants of effective follow-up. In Greece and Poland, where most of recruitment and follow-up took place, GPs said that younger and more educated people used the apps successfully to report their PROM, while older participants who were less familiar with new technologies or did not know how to use computers were confused and occasionally entered incorrect responses or did not submit their PROM.

Technical barriers also hindered effective follow-up. GPs in Poland said that some patients did not have an email account (also the case in the UK and Greece) or did not remember their email; others did not check their email account regularly; some patients never received an email because the email
provided was incorrect (typos); while others ignored it as the subject and sender fields resembled spam email and were afraid of getting a virus. Also, the username was 30-40 characters long and patients had trouble logging in. As a result, some failed to submit their PROM correctly and were advised to visit the clinic and complete their PROM with some help from the practice staff. Some did, but others did not, resulting in loss to follow up.

The effectiveness of follow-up was also limited by the inability of GPs to monitor the whole process. GPs could not see whether a patient had completed their PROM until visit 2 (if the patient had not completed their PROM by the follow-up visit, the GP would not be able to access the forms and record CROM data for visit 2). This was thought to hinder effective follow-up.

Cultural barriers were also identified in some cases. In Poland, patients with no access to a computer or email account were invited to complete their PROM at the clinic. Some patients did not follow up because they felt embarrassed for being unable to complete their PROM using the apps, which may explain some of the attrition in the TRANSFoRm arm. It was also reported that a small number of patients were also worried about the confidentiality of information in the questionnaires and the risk of unauthorised access to private data by non-clinical staff (e.g. members of the TRANSFoRm project).

Areas for improvement and recommendations

The main advantage of TRANSFoRm compared with existing methods is that it enables pre-population of eCRFs using data from the patient’s electronic health record, saving time for GPs and patients by eliminating the need for double data entry. However, this advantage was not realised in this study as only a few variables were extracted (age, gender, medication, BMI) from the eHR. For TRANSFoRm to perform optimally, data will need to be coded well enough to support pre-population of eCRFs.

The TRANSFoRm system should support offline operation to allow GPs to recruit patients when there is no internet connection. The system should also be flexible to include patients who were excluded for non-study related reasons, such as insurance status in Greece, and allow GPs to edit study forms. It could also be smarter to group questions together and hide/show questions based on previous answers, intuitive enough to reduce the need for training and IT proficiency given the stressful and time-pressured environment within which recruitment takes place, and include data analytics functionality to enable statistical analysis at the GP level.
Implementation of the programme was considered very important. GPs are not computer experts and should be given sufficient time to become familiar with the system and local ICT support before, during and after implementation. The GP from The Netherlands said that, when sought ICT support, there were many persons involved from different countries (The Netherlands, Poland and the UK), resulting in excessive amount of time to troubleshoot. Therefore, the GP suggested a longer testing period (3 months) before the system is launched in everyday practice as the acceptance for glitches is low among busy practitioners.

GPs also suggested changing the recruitment process to introduce a separate appointment for consent and CROM data collection by another health professional to make the whole process easier and more efficient. In the UK, for instance, there was not enough time to check eligibility, explain the study, obtain consent and collect CROM data in a busy surgery with a 10-minute consultation per patient.

The follow-up process also requires improvement. GPs said that they would like to receive a notification alert or email when participants do not complete their PROM to be able to follow up with them separately. In the control arm, GPs could monitor the whole process as the surveys were mailed directly to the practice and could check who had or had not completed their PROM. This was not possible in the TRANSFoRm arm.

GPs also suggested to update the sender and subject fields in the follow-up email and to include detailed instructions on how patients should use the apps to complete their PROM. They also proposed to shorten the username which was way too long (30-40 characters) and caused login problems, especially among older patients who did not know how to copy and paste. Finally, GPs recommended to make the automatic log off timer more visible as some patients did not notice that they had 20 minutes to fill out the form and they had to rush, which often caused frustration and may have led to incorrect entries.

**Patients’ experiences**

**Recruitment process**

Patients visited their GP for their routine consultation. The GP discussed the study and asked them to sign a consent form. They then went through the eligibility criteria and the GP completed the CROM using the TRANSFoRm system. The GP then explained that patients would receive an email with a link to complete their PROM using the TRANSFoRm apps. None of the participants had previous experience from another study and found it difficult to compare the TRANSFoRm recruitment process with standard practice. Overall, they were satisfied with the recruitment process, although
one participant felt that the questionnaires were complex and long and suggested asking less questions.

**Follow-up process**

Participants received an email with a link to complete their PROM. They then used the TRANSFoRm web app to enter their data. Participants did not show a preference toward a specific method. If they were given the option, three said they would prefer to use the TRANSFoRm app because it provided an easier and faster way to complete their PROM compared with paper-based questionnaires; three did not show a preference towards a particular method; and one would prefer to complete the PROM manually at the GP clinic. This was due to login problems that the participant experienced before finally managing to fill out the PROM and the design of the app that hinders users from entering free-text comments.

**Strengths and weaknesses of TRANSFoRm app**

All participants agreed that the TRANSFoRm web app is easy to use. However, a participant also said that the app may not be suitable for older people who are not familiar with new technology.

**Areas for improvement and recommendations**

One participant suggested to include a free text field for patients to comment as they would do using paper and pen. The patient also thought that follow-up for older people should be done at the clinic partly because personal contact with the doctor is crucial for this group of patients and partly because it is hard for older people to use electronic tools.

**2.2.6.45 Technology acceptance**

Only 12 patients answered the TAM survey. Because of the low response rate we will not present the results.

**2.2.6.5 Economic evaluation**

Overall, the TRANSFoRm system performed similarly to existing systems. In the Netherlands, the GP reported that it took about 20 minutes to recruit a patient (i.e. go through the inclusion/exclusion form, obtain informed consent and collect CROM data) and this did not differ from the control arm according to the research assistant who facilitated the recruitment interviews with eligible patients in the control arm. The follow-up visit took about 5-10 minutes per patient, independent of arm. In the UK, the GP said that it took approximately 10 minutes to explain the study and seek patient consent, which was similar to the control arm. In Greece, GPs said that it took about 10-20 minutes
to determine eligibility and another 10-15 minutes to explain the study and collect informed consent depending on the patients’ symptoms, medical history, age and number of questions asked (total time 20-35 minutes). In Poland, GPs did not specify the duration of recruitment. However, patients reported that PROM completion in the TRANSFoRm arm took between 8 and 20 minutes. Prior to the study, it was estimated that the PROM surveys would take about 20 minutes to fill out.

2.2.7. Comments

There were no difference in recruitment rate between the TRANSFoRm arm and the control arm. The completion rate for the CROM was significantly higher in the TRANSFoRm arm, while the completion rate for the PROM was significantly higher in the control arm. There were no differences in the time taken to recruit a patient between arms. Technical, cultural and implementation barriers were identified by GPs in the follow-up interviews that could be solved in future developments of the system and further improve the efficiency of the system. In spite of the issues brought up during the interviews, TRANSFoRm was considered the preferred method for CROM data collection compared to existing methods by the majority of the interviewed GPs.

The initial aim of the use case was not to deliver a full RCT to test the clinical research question but to demonstrate the ability of TRANSFoRm to run an RCT and to deliver a proposal for full implementation of the definitive study, due to ethical constraints, where we had to run a fully powered clinical trial to be able to get ethical approval for the study. In the RCT we recruited more than 600 patients bringing us close to the goal of 700 recruited patients. However, the meta-RCT evaluation study became underpowered compared with our initial plans as no data was contributed to the analysis from the UK (2 sites, 20 practices) or The Netherlands and 8 rather than the 23 planned pairs of practices included in the analyses. Albeit all systems were GCP certified before the start of the study, there were technical difficulties that affected the practices at the start of the study. Installed software required configuration to match the environment in which it was placed and that environment was not always stable over time and its relationship to the configuration was not always understood by installers. In Poland, these difficulties in combination with holidays for the GPs delayed the start of the patient recruitment for several weeks.

One common issue was the lack of notification to the GP to see that the PROM had been completed by the patient and this was believed to contribute to participants being lost to follow-up. However, most eHR systems involved in TRANSFoRm were unable to respond to notifications from the TRANSFoRm platform including the ability to view previously stored forms, although the platform does support this. The TRANSFoRm study monitoring workbench can only report numbers of
completed PROM per practice as the TSS does not contain information about the identity of a patient that is recognizable by the study personnel and hence cannot display such information to highlight a missing PROM. This is in sharp contrast to the paper questionnaires that were collected by the primary care personnel directly and likely explains why the completion rate of PROM in the control arm was higher than in the TRANSFoRm arm. A few GPs also asked for access to the PROM. This was one of the functionalities listed at the beginning of the project but was not enabled in some versions of the system as only the UK vendors implementations could have responded to such a notification from the DNC and the functionality was dropped on account of resource constraints and the desire to avoid upgrading installations already in use. In some of the localities, questionnaires were not completed in the predefined order, the withdrawal form was occasionally filled out by mistake, and the CROM form was sometimes filled out multiple times. Although the study definition model specified the correct ordering of forms and that information was transmitted to the eHR vendor systems, it was not acted on. This arose mostly because vendor developments started before definition and completion of certain aspects of the platform and there was no desire on the part of the vendors to ‘revisit’ existing developed code. At times the local connection between the eHR system and the DNC was lost which meant that the TRANSFoRm eCRF tool could not be used. This could happen when the network environment changed locally and no corresponding change was made in the DNC configuration. The eCRF tool could also fail if some component of the overall platform was not available, such as the semantic mediation service. In retrospect, many of these technical issues arose and remained because software development was not initiated early enough within the project. Also, centralised, continuous monitoring of platform components and local DNC installations would have helped ensure a more reliable experience for users. Finally, an online help system to improve support and regular brushing up of training might have decreased the impact of this issues on the data collection.

Comments from patients also related to log in difficulties with mobile applications where user credentials were very long. This has a potentially easy solution by providing a link to the specific account in the email. In a few cases, the study emails ended up in the SPAM folder, and care should be taken to avoid key words in the email that increases the likelihood that an email is marked as spam. The use of unverified email addresses resulted in a few patients not being reached by the study emails. In subsequent versions of the system, a procedure to verify email addresses at inclusion should be included in the inclusion process and online services are available for this purpose.

Apart from these glitches, the GPs reported that they found the system easy to use and especially liked the functionality of flagging patients which currently is the major functionality that sets the
TRANSFoRm system apart from other eCRF tools. As one GP pointed out, the TRANSFoRm system is depending on well coded data in the eHR to be able to prepopulate the fields in the CROM forms. As the structures of medical records are improving, the usefulness of the functionality of prepopulated fields will increase with time.

The number of recruited patients was low in The Netherlands and the UK. The timing of the study was unfortunate considering difficulties within the National Health Services in the UK that made it difficult for participating practices to prioritize the study. In addition, a large proportion of the patients that were approached in the UK said that they did not want to take PPI on demand and thus declined participation in the study. In The Netherlands a different approach was used as there were few practices using the chosen eHR system and to be able to recruit sufficient number of practices, one GP and one research assistant did all the recruitment interviews and data entry. In addition, all eligible patients identified by a search at the practices were invited by post. This should have led to the invitation of a large number of patients in The Netherlands. However, the protocol for treating GORD with PPI is slightly different in The Netherlands, and a majority of the patients were taking 40 mg omeprazole daily and could not be included in the study.

A major problem for the study was that there is not enough time to provide study information, collect informed consent and fill out CROM in one standard consultation. All GPs that were interviewed stated that the administration around the inclusion of the patient took up to 30 minutes. A future enhancement to enable greater flexibility in the recruitment process would be to support multiple users during a consultation, for example enabling both a practice nurse and GP to interact with the patient during the same visit to the practice. In this way we could match appropriate users to different parts of the recruitment process and GP time could be kept to a minimum. For example, the practice nurse could check eligibility and provide study information in advance of the patient seeing the GP and have this recorded.

2.2.8. Conclusion

In conclusion, our study suggests that the TRANSFoRm system was as efficient as manual recruitment of patients, but also the preferred method of recruitment among GPs. No conclusive evidence can be drawn about the cost-effectiveness of TRANSFoRm for conducting trial recruitment and follow-up in primary care. The meta-RCT demonstrated that the TRANSFoRm system can be used to perform a clinical trial in primary care in several localities across Europe. It identified a number of issues to be solved in the next version of the software that is likely to increase its effectiveness and the new
version needs to be tested in a similar but larger meta-RCT to demonstrate its superiority to current methods for recruitment and data collection in clinical trials in primary care.
3. References


Appendix

A: Validation study paper/publication (Mastellos, Blizniuk et al. 2015).

B: Evaluation protocol paper/publication (Mastellos, Andreasson, et al., 2015).

C: TAM Participant survey
Appendix

A: Validation study paper/publication (Mastellos, Blizniuk et al. 2015).
Qualitative Research

Feasibility and acceptability of TRANSFoRm to improve clinical trial recruitment in primary care

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Abstract

Background. Recruitment of study participants is a challenging process for health professionals and patients. The Translational Medicine and Patient Safety in Europe (TRANSFoRm) clinical trial tools enable automated identification, recruitment and follow-up in clinical trials, potentially saving time, effort and costs for all parties involved.

Objectives. This study evaluates the acceptability and feasibility of TRANSFoRm to improve clinical trial recruitment in primary care.

Methods. A feasibility study was conducted in three general practices in Poland. Participants were physicians and patients with gastro-oesophageal reflux disease. Semi-structured interviews were held to obtain feedback about the usefulness, ease of use and overall experience with the TRANSFoRm tools and to identify potential usability issues. Data were analysed thematically.

Results. A total of 5 physicians and 10 patients participated in the study. Physicians were satisfied with the usefulness of the system, as it enabled easier and faster identification, recruitment and follow-up of patients compared with existing methods. Patients found the TRANSFoRm apps easy to use to report patient outcomes. However, they also felt that the apps may not be useful for patients with limited exposure to smartphone and web technologies. Two main usability issues were identified: physicians could not access the result of the randomization at the end of each visit, and participants could not locate the follow-up reminder email.

Conclusions. This study provides new evidence on the acceptability and feasibility of TRANSFoRm to enable automated identification, recruitment and follow-up of study participants in primary care trials. It also helps to better understand and address users’ requirements in eHealth-supported clinical research.

Key words. Electronic medical records, gastroenterology/GERD/dyspepsia, primary care, quality of life, research ethics/informed consent.
Feasibility and acceptability of TRANSFoRm

Introduction

Randomized controlled trials (RCTs) provide a powerful study design for the evaluation of health care interventions and have been widely accepted as the gold standard of clinical research. However, many studies fail to reach their pre-specified sample targets within the planned timeframe and budget. A recent review of 114 trials in the UK found that only 31% met their original recruitment targets, while 53% achieved their goals after extending the length of the trial (1). Similarly, a study of 41 trials in the USA found that only 34% achieved or exceeded their targets, while 24% failed to recruit more than half of their original sample size (2). This is particularly worrying because usually clinical trials succeed or fail based on whether they are powered enough to test the efficacy of a drug, medical device or health intervention. Low recruitment is often addressed by extending the length of a trial until the required sample size is reached. However, this creates extra costs for funders and results in delays in the rollout of potentially effective interventions (3). Recruitment of study participants in primary care poses additional challenges and can be particularly problematic in international and/or cross-national, multicentre studies when multiple practices are involved (4,5). Primary care recruitment takes place in a highly stressful and time-pressured environment, where busy physicians approach eligible patients directly within their consultations and invite them to take part. As a result, recruitment can be slow with physicians often failing to translate the initial enthusiasm into recruitment targets (6).

Despite significant advancements in information technology, recruitment remains a highly laborious and time-consuming process. The increased adoption of electronic health record (EHR) systems in primary care offers the opportunity for real-time identification, recruitment and follow-up of study participants. Eligibility criteria can be checked without disrupting the clinician’s workflow, by querying the EHR of the presenting patient. Electronic case report forms (eCRF) can integrate with EHR systems to support automated data collection of elements present in the patient’s EHR, thereby increasing data quality and completeness and reducing the time and costs of recruitment (7,8). Electronic patient-reported outcome measures (ePROM) apps enabling data collection either via the web or via the participant’s smartphone can further increase the accuracy, completeness and timeliness of data in clinical research (9,10).

The Translational Medicine and Patient Safety in Europe (TRANSFoRm) project team have developed a digital platform to support clinical trial recruitment in primary care. Figure 1 shows the TRANSFoRm clinical trial workflow and the system components involved. These include an enhanced EHR System Interface; a TRANSFoRm Forms Interface for clinician-reported outcome measures (CROM) data collection; a TRANSFoRm compliant Study System that stores the study definitions and collected data; and a component known as Data Node Connector (DNC), which mediates the interaction of the other three. The enhanced EHR System Interface, Forms Interface and DNC are collectively known as the TRANSFoRm eCRF tool. Patient-reported outcome measures (PROM) data, collected via the TRANSFoRm web or mobile apps, are incorporated into the eCRF tool. At study completion, data are exported to the researcher for analysis.

In the scenario used in this study, patients with gastro-oesophageal reflux disease (GORD) visit their doctor for their routine consultation (Fig. 1). Forms used in the GORD study are highlighted with black boundaries. Potential participants are identified by TRANSFoRm after checking for GORD diagnosis, symptoms and/or treatment prescriptions. Then, the physician checks for the first set of study criteria and, if the patient is eligible and willing to participate, collects informed consent. Next, CROM data from the patient’s EHR are extracted to populate fields in the participant’s eCRF and the system presents the CROM dataset to the physician for approval. TRANSFoRm then randomizes participants and reports allocation instantly to enable initiation of the study intervention. PROM data are incorporated into the eCRF via the TRANSFoRm apps. Researchers can monitor the study status through an interface of the Study System, but they do not have access to study data. Upon study completion, the study dataset is delivered to the researcher through a secure data transport mechanism.

This study assesses the acceptability and usability of TRANSFoRm from the point of view of the physician-recruiter and GORD patient-participant. The effectiveness of TRANSFoRm will be evaluated in a cluster RCT investigating the question ‘what gives most symptom relief and improvement in quality of life in patients with Gastro-Oesophageal Reflux Disease (GORD), on demand or continuous use of proton pump inhibitors?’ (11). Results from the trial will be published separately.

Methods

Study aim and objectives

This study examines physician and patient acceptability of TRANSFoRm with the aim to confirm its feasibility to perform clinical trial recruitment and follow-up in primary care. A secondary aim is to identify potential usability issues prior to the summative evaluation of the tools in the cluster RCT.

Study setting and participants

The study took place in Poland in May 2015. Participants were physicians and patients with GORD. To be eligible, practices had to (i) use a mMedica EHR system, (ii) nominate one or more physician to participate, (iii) be willing and able to identify suitable study participants and (iv) provide informed consent. Patients were eligible if they were (i) 18–65 years old, (ii) had a GORD diagnosis and/or proton pump inhibitor prescription within the last 12 months, (iii) were willing to complete PROM data in electronic format and (iv) provided written informed consent.

Between December 2013 and April 2014, scientific personnel from ASSECO, a big EHR vendor in Poland, invited all mMedica practices (n = 9420) to participate in the TRANSFoRm cluster RCT. Invitations took the form of pop-up messages on mMedica systems and letters to the practices that expressed initial interest in participating. Fifty-eight practices responded positively. However, only 24 had a mMedica system with a cabinet module installed, which is a prerequisite for the implementation of TRANSFoRm, and therefore were considered for inclusion (see online Supplementary File 1). A total of 10 practices, which best fulfilled the trial’s practice eligibility criteria (11) and were able or willing to commit to the study protocol requirements, were selected for the trial. Of these, three were invited to participate in the study described here. The selection was based on their readiness to implement the TRANSFoRm system at the time of the study.

Usability studies need five users to discover about 85% of usability problems with a system interface (12). This level of problem discovery was acceptable considering the well-focused nature of the test, the focus of the study on high-severity problems and the budget limitations. Three systems were tested: (i) eCRF tool for physicians; (ii) web app for patients and (iii) mobile app for patients. Therefore, 5 physicians and 10 patients were invited to participate.
All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

Intervention

The intervention was delivered in a controlled, real-life setting. Physicians used the TRANSFoRm eCRF tool to recruit eligible GORD patients and collect baseline data. GORD patients, aged 18–65 years old, visited their doctor and went through the recruitment steps described in the TRANSFoRm study workflow (Fig. 1). Once recruited, patients were invited by email to use the mobile or web app to fill out and submit PROM data (e.g. Quality of Life questionnaire). Prior to intervention delivery, face-to-face training was provided to all physicians by qualified study personnel. Patients did not receive any training because the apps were designed to be intuitive to eliminate the need for training in a real-life trial. All tools were installed and tested by qualified scientific personnel from the Centre for Health Information Systems (CSIOZ) and developers from ASSECO in collaboration with the TRANSFoRm project team between January and March 2015.

Data collection

Following recording of CROM/PROM data, semi-structured interviews with physicians and study participants were conducted by a qualified researcher from CSIOZ. The interviews explored users’ self-efficacy and perceptions about the usefulness, ease of use, design, usability and overall experience with TRANSFoRm (see online Supplementary Files 2 and 3). Each interview lasted for ~30 minutes. At the participants’ request, all interviews were recorded using paper and pen, transcribed verbatim and translated into English by qualified bilingual personnel.

Data analysis

Interview data were analysed thematically in English using the Ritchie and Spencer’s Framework Approach (13). The analysis was performed by the researcher who collected the data and two independent researchers from the Medical University in Wroclaw and Imperial College London. This included a series of well-established steps to ensure consistency, credibility and traceability of findings. First, analysts familiarized themselves with the data by reading and rereading the transcripts and jotting down notes. Second, they developed a thematic framework by identifying a priori themes from the interview guide, emergent issues raised by the participants and analytical themes arising from the recurrence of particular experiences. Third, analysts applied the framework to the data in its textual form using index prefixes and annotations. Then, they formed charts by rearranging the data according to major thematic categories from the framework and, finally, pulled together the data to interpret the whole dataset and provide explanations for the findings (13). Any discrepancies were resolved by consensus or discussion with a fourth researcher from Karolinska Institutet.

Results

Demographics

Five physicians and 10 patients from 3 practices in 3 cities (Mielec, Piotrków Trybunalski and Łódź) participated in this study. Mielec participated with two physicians and five patients; Piotrków Trybunalski with one physician and three patients and Łódź with two physicians and two patients. The physician group consisted of two male and three female physicians with an average age of 49 years. The GORD patient group had a mean age of 48 years and included six male and four female participants. No further demographic and socio-economic data were collected for the purpose of this study.

Physician acceptability

Overall, physician acceptability of the TRANSFoRm eCRF tool was positive. Respondents highlighted the role of training in increasing confidence with using the system and identified a number of advantages compared with standard practice (Table 1).
Self-efficacy
Physicians felt that the system requires some skill to use. The training lasted for approximately an hour. All physicians said that the training was satisfactory and equipped them with the necessary skills to perform patient recruitment.

Usefulness and ease of use
Physicians found the system simple and easy to use. Particularly, they said that identification of potentially eligible patients was quick; randomization and allocation of study participants were simple and data collection and submission were easy. Respondents felt that TRANSFoRm could enable them to recruit patients in an easier and faster way compared with standard practice.

Usability issues
One main usability issue was identified. Physicians said that they would like to access all patient forms at the end of the visit, especially the form with the randomization result, to be able to confirm each individual randomization, as per the study protocol. All study forms were automatically stored into the Study System. However, with mMedica EHR, no client interface mechanisms were provided to permit these forms to be viewed. Therefore, physicians had to manually record this information.

Patient acceptability
Patients expressed a positive opinion about the usability of the TRANSFoRm ePROM apps. However, they also identified some areas for improvement (Table 2).

Table 1. Thematic analysis of physician acceptability of the TRANSFoRm eCRF tool among five physicians from three general practices in Poland in May 2015

<table>
<thead>
<tr>
<th>Theme</th>
<th>Quote from the interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient training and confidence</td>
<td>GP03: ‘Yes, there was training provided and lasted for approximately an hour. It requires skills to operate the program. The training was sufficient at this stage’.</td>
</tr>
<tr>
<td>Adequate user-friendliness</td>
<td>GP01: ‘The system is easy and simple. I had no problems using the system for all aspects of recruitment’.</td>
</tr>
<tr>
<td>Improved recruitment efficiency</td>
<td>GP04: ‘Recruiting patients using the electronic health record system is faster and easier’.</td>
</tr>
<tr>
<td>Lack of access to the randomization forms</td>
<td>GP02: ‘After the finish of the first visit all forms disappear, especially one with randomization result. It’s worth leaving those forms in the view mode for doctor to be able to look there to see the history of the patient. I wanted to look at the randomization form, but it wasn’t possible as the first visit was already finished’.</td>
</tr>
</tbody>
</table>

Table 2. Thematic analysis of patient acceptability of the TRANSFoRm ePROM apps among 10 patients from three general practices in Poland in May 2015

<table>
<thead>
<tr>
<th>Theme</th>
<th>Quote from the interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for training for unexperienced users</td>
<td>PAT06: ‘Overall, everything is fine. I had no problems with filling the form. Navigating the app was easy. Older people may need help from family members. Smartphone apps are for young people. Older people may have trouble using them’.</td>
</tr>
<tr>
<td>Poor communication of medical terminology</td>
<td>PAT09: ‘It is necessary to explain medical terms to the patient. If the patient doesn’t know anatomy, they might have problems with some definitions’.</td>
</tr>
<tr>
<td>Contrasting views on usefulness</td>
<td>PAT08: ‘The data was entered using the computer. There were no problems. The app is easy to use and was able to fill out the questionnaire in a timely manner’. PAT04: ‘It is much easier to fill the form on paper. The computer is not needed here’. PAT08: ‘I see no difference in filling out the questionnaire using the app or paper’.</td>
</tr>
<tr>
<td>Need for better follow-up instructions</td>
<td>PAT05: ‘I failed to open the app. The e-mail was received, but it didn’t work. I tried to open the web PROM in Google Chrome. It was too complicated to log into the system. I tried to use several computers within the last three days. Every time I used Google Chrome and once Internet Explorer. The link was not working and there was a message on the screen that access is blocked’.</td>
</tr>
</tbody>
</table>
Conclusions

The widespread use of EHR systems in primary care offers the potential to electronically identify, pre-screen and follow-up patients using EHR flagging and data collection tools. This study provides evidence on the physician and patient acceptability of such tools using the example of TRANSFoRm. The findings demonstrate the feasibility of TRANSFoRm to improve the conduct of clinical research in primary care by reducing the time and effort required by physicians and patients to perform recruitment and follow-up. Time and effort are significant determinants of physician and patient participation in research (14–16). Improvements in participation and therefore recruitment can help researchers to collect sufficient data to precisely and reliably answer their research questions and clinicians to use this data to take clinical decisions and improve care and patient safety.

In line with previous research, our findings show that EHR flagging and data collection tools are well accepted by clinicians and patients. In a similar study in the UK, the EHR system was used by physicians to identify eligible patients during the consultation, confirm eligibility and collect follow-up data on major clinical outcomes. Both patients and physicians perceived the use of EHR-based tools as an acceptable and feasible method for participant recruitment and follow-up (17). In another study, the use of clinical trial alerts for the identification of patients whose EHR data met specific eligibility criteria resulted in increased physician participation, recruitment efficacy and satisfaction, despite the often intrusive nature of alerts (18). Previous research has shown that physicians often find the pop-up alerts disruptive and frequently ignore them due to lack of time in the consultation (19). In this study, physicians did not feel this way, but it is unclear whether this was due to the high sensitivity and specificity of the system or the controlled nature of the study.

The results also suggest that participants, especially those with limited exposure to smartphones and/or the Internet, should be given clear instructions on how to access and use the apps online and/or the option to fill out their questionnaires using paper and pen. Training will be necessary to support users with little or no previous experience with smartphones, tablets or computers. Clear instructions on how to access and complete a study questionnaire online should be provided to all participants. In this study, a significant amount of patients failed to provide PROM data as part of the usability study because they lacked instructions on how to locate or open the link that was sent via email.

The study has some limitations. First, the sample size was relatively small to generate fine-grained themes. However, considering the exploratory aim of the study and the homogeneity of participants, the sample was sufficient to discover high-severity usability problems and develop high-level themes (12,20). Second, the interviews were conducted in Polish and translated into English by bilingual personnel. Despite efforts to translate verbatim into English, it is possible that some content was not translated precisely. However, it is unlikely that this has influenced the interpretation of data. Finally, the aim of this study was to assess the acceptability of TRANSFoRm and its feasibility to improve recruitment in primary care trials. Therefore, no conclusive evidence can be drawn about the ability of the system to improve the efficacy and cost-effectiveness of clinical research. The efficacy of the tools will be evaluated in a cluster RCT with the participation of 40 general practices from 5 countries (11). By identifying usability issues and by providing recommendations for improvement, the current study helps to better understand and address the needs of different users in eHealth-supported clinical research.

Supplementary material

Supplementary material is available at Family Practice online.

Declaration

Funding: European Commission’s Seventh Framework Programme for research, technological development and demonstration under grant agreement number 247787.

Ethical approval: Bioethics Committee of the Lower Silesian Chamber of Physicians in Wroclaw (Ref. 2/NT/2014).

Conflict of interest: none.

References

17. van Staa TP, Dyson L, McCann G et al. The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected data.


Appendix

B: Evaluation protocol paper/publication (Mastellos, Andreasson, et al., 2015).
A cluster randomised controlled trial evaluating the effectiveness of eHealth-supported patient recruitment in primary care research: the TRANSFoRm study protocol

Nikolaos Mastellos¹*, Anna Andreasson², Kit Huckvale¹, Mark Larsen¹, Vasa Curcin³, Josip Car¹, Lars Agreus² and Brendan Delaney³

Abstract

Background: Opportunistic recruitment is a highly laborious and time-consuming process that is currently performed manually, increasing the workload of already busy practitioners and resulting in many studies failing to achieve their recruitment targets. The Translational Medicine and Patient Safety in Europe (TRANSFoRm) platform enables automated recruitment, data collection and follow-up of patients, potentially improving the efficiency, time and costs of clinical research. This study aims to assess the effectiveness of TRANSFoRm in improving patient recruitment and follow-up in primary care trials.

Methods/design: This multi-centre, parallel-arm cluster randomised controlled trial will compare TRANSFoRm-supported recruitment with standard opportunistic recruitment. Participants will be general practitioners and patients with gastro-oesophageal reflux disease from 40 primary care centres in five European countries. Randomisation will take place at the care centre level. The intervention arm will use the TRANSFoRm tools for recruitment, baseline data collection and follow-up. The control arm will use web-based case report forms and paper self-completed questionnaires. The primary outcome will be the proportion of eligible patients successfully recruited at the end of the 16-week recruitment period. Secondary outcomes will include the proportion of recruited patients with complete baseline and follow-up data and the proportion of participants withdrawn or lost to follow-up. The study will also include an economic evaluation and measures of technology acceptance and user experience.

Discussion: The study should shed light on the use of eHealth to improve the effectiveness of recruitment and follow-up in primary care research and provide an evidence base for future eHealth-supported recruitment initiatives. Reporting of results is expected in October 2015.

Trial registration: EudraCT: 2014-001314-25

Introduction

Background

Recruitment to primary care trials is a particularly challenging process with most studies struggling to reach their recruitment targets. In fact, a survey of authors of 39 published primary care trials found that only 29% of UK primary care studies achieved their recruitment targets within the agreed timeframe, with 70% requiring additional time to recruit the predefined number of participants [1]. This is very worrying considering that clinical trials succeed or fail based on whether they manage to recruit the sufficient number of participants to enable researchers to generate accurate results to precisely and reliably answer the question at hand. Recruitment failings can result in studies lacking statistical power to produce significant results, increasing the risk that an effective health intervention will be abandoned before its real impact has been demonstrated [2]. Consequently, improving

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the recruitment process in clinical trials is extremely important for the future of medical research.

Evidence suggests that the most effective method of recruitment in primary care is opportunistic recruitment [3]. This involves approaching eligible primary care patients when they visit their general practitioner (GP) and inviting them to take part. Opportunistic recruitment takes place in a highly stressful and time-pressured clinical environment and relies on busy GPs directly inviting patients within the consultation [4]. As a result, this method can be very challenging and slow with practitioners often failing to translate the initial enthusiasm into recruitment targets [5].

The increased adoption of electronic health records (EHR) systems in primary care provides the opportunity for real-time identification of eligible participants through the use of clinical trial alert systems [6-9]. Such systems notify GPs about eligible patients during the consultation allowing them to immediately discuss the trial with the patient to enable instant recruitment, thus negating the need for laborious effort on the part of the practitioner, patient or researcher [10]. The Translational Medicine and Patient Safety in Europe (TRANSFoRm) project team has developed a suite of software tools and underlying infrastructure to support patient recruitment to primary care studies across multiple sites and countries, potentially saving time for busy practitioners and patients in the consultation room [11]. This protocol describes a cluster randomised controlled trial evaluating the effectiveness of the TRANSFoRm system in improving patient recruitment and follow-up in primary care trials.

The TRANSFoRm system supports secure, provenance-enabled design, deployment and collection of patient-reported outcome measures (PROM) and electronic case report forms (eCRF) through web and mobile applications as well as EHR systems in the primary care centres where the trials are taking place, as shown in Figure 1. The GP-facing tools enable automated identification, eligibility check, randomisation, baseline and follow-up data collection and reporting of data in clinical studies, while the patient-facing tools support collection of patient-reported data through mobile or web applications.

Figure 2 shows the TRANSFoRm-supported clinical trial workflow, starting with a patient visiting their GP for their consultation. Potential participants are identified using a clinical trial alert tool that notifies the GP that the patient fulfils specific inclusion criteria, after checking for diagnoses, symptoms and/or treatment prescriptions. Once identified, the GP can check for the first set of inclusion and exclusion criteria and, if the patient is still suitable, collect informed consent for further screening. Next, clinical data from the patient’s electronic record is extracted to populate fields in the eCRF. The system alerts the practitioner about any missing data and presents the study dataset for final approval. PROM data is incorporated into the eCRF via a web or mobile application used by participants to record symptoms, signs and other self-reported outcomes. The system randomises enrolled patients and reports allocation instantly so that the study intervention can be initiated without delay. Participants are then followed up using the mobile or web applications and the eCRF tool at GP visits. Following GP approval, the study dataset is delivered to the researcher through a secure data transport mechanism that communicates with TRANSFoRm connector tools on the participating EHR.

The development of the clinical study workflow has been structured around a clinical study which acts as a use case for the evaluation of TRANSFoRm. The gastroesophageal reflux disease (GORD) study employs a randomised controlled trial design to answer the following question: “What gives most symptom relief and improvement in quality of life in patients with GORD, on demand or continuous use of proton pump inhibitors?”. Participants will be patients with GORD, aged 18–65 years old. The study will take place in five countries and will involve 16-week recruitment and 8-week follow-up. The follow-up time was chosen because proton pump inhibitor (PPI) treatment is known to have an effect after 2 weeks. Therefore, 8 weeks should be sufficient to
detect any changes in symptoms and quality of life. The role of TRANSFoRm in this study is to identify prevalent and incident cases of GORD, randomise patients to on-demand or continuous use of PPI and follow up these patients using mobile or web applications and eCRF completed by GPs at primary care visits. Further details about the clinical study will be provided in a separate publication.

Aim and objectives

The study described in this protocol aims to assess the effectiveness of TRANSFoRm in patient recruitment compared to standard GP-led opportunistic recruitment. The study hypothesis is that TRANSFoRm will increase patient recruitment by 15%, from 20% to 35%, compared to standard practice.

The objectives of the study are:

1. To evaluate the effectiveness of TRANSFoRm in recruiting patients to clinical trials.
2. To assess its effectiveness in collecting complete baseline and follow-up data.
3. To compare the costs of recruitment in the TRANSFoRm and control arms.
4. To explore practitioner and patient experience and acceptability of the system.

Methods/design

Trial design

We plan to conduct a 24-week, multi-centre, parallel-arm cluster randomised controlled trial of TRANSFoRm recruitment compared to GP-led opportunistic recruitment. The intervention arm will use the TRANSFoRm tools for participant recruitment, baseline data collection and follow-up. The control arm will rely on standard GP-led recruitment using web-based CRFs for baseline data collection and paper-based questionnaires for follow-up. The study will run in five countries (United Kingdom, The Netherlands, Belgium, Poland, and Greece) with eight primary care centres in each country, giving a total of 40 centres. Of these, 20 will be randomised to the TRANSFoRm arm and 20 to control on a 1:1 allocation ratio. Potentially eligible participants will be identified and recruited using TRANSFoRm or standard GP recruitment, with the hypothesis being that TRANSFoRm will yield 35% recruitment rate compared to 20% for the standard method. Participants will be finally randomised to on-demand or continuous use of PPI as part of the clinical protocol for the GORD study (Figure 3).

Participants

The intervention will be implemented at the primary care centre level. To be eligible for participation, primary care centres should use an EHR system compatible with TRANSFoRm, provide written agreement to participate in the GORD study, agree to participate in whichever arm they are randomly allocated, have a list size of over 2,000 patients and be able to identify at least 100 eligible participants over the 16-week recruitment period. Primary care centres lacking an appropriate EHR system or centres that have migrated from paper-based record keeping within the last 12 months will be excluded. Primary care centre characteristics, such as list size and GORD prevalence, will be gathered from GP database audit to inform recruitment. Local project partners will liaise with the study coordinator to recruit care centres that meet the above criteria.

Study participants will be GPs located in primary care centres receiving the TRANSFoRm intervention or standard recruitment method, and GORD patients using the web/mobile- or paper-based method for recording self-reported data. To be eligible for participation, patients should be GORD cases with heartburn and/or acid regurgitation that need PPI treatment, aged 60–85. Pregnant women, patients with a myocardial infarction within 6 months of the study.
commencement or patients with serious comorbidity will be excluded from the study. Informed consent will be sought from all sites. Primary care centres will provide informed consent as a unit. This may vary from all GPs signing the consent form to one GP being authorised to sign on behalf of the centre. Patients will consent in accordance with the requirements of the GORD trial. The participating centres will receive €17 compensation for each correctly enrolled patient. Patients will not receive any incentive for taking part. Participants are not expected to experience any harm as a result of their participation in the evaluation study, as their involvement is restricted to completing the PROM questionnaires. Despite including health information, it is unlikely that these questionnaires will address any sensitive issues.

**Setting**
We aim to recruit 40 urban, suburban and rural primary care centres in and around five European sites: London (United Kingdom), Utrecht (The Netherlands), Antwerp (Belgium), Wroclaw (Poland) and Heraklion-Crete (Greece). A dedicated member of the study team will liaise with local coordinators in each country to recruit eligible practices. Detailed practice characteristics will be provided in future publications.

**Intervention and control**
Primary care centres allocated to the intervention arm will use the TRANSFoRm tools for participant recruitment, baseline data collection and follow-up. When visiting their GP, potentially eligible patients will be flagged by the system so that their GP can check for the first set of inclusion and exclusion criteria and, if appropriate, collect informed consent for further screening. Next, clinician-reported outcome measures (CROM) data from the patient’s health record will populate fields into the patient’s eCRF. The system will notify the GP about any missing data. Upon GP approval, the system will randomise patients to on-demand or continuous use of PPI. Participants will then receive information on how to fill out the PROM fields on their smartphone or the web. When participants return for the follow-up visit after 8 weeks, as stipulated in the clinical protocol, the CROM data is activated; the GP checks all prefilled fields and adds any missing data. If the participant does not attend the second visit, the GP will receive a reminder. PROM data is provided by the participants within 3 days from the second visit using the mobile/web application. Participants will receive reminders 2, 3 and 4 days after the visit, if the self-reported data is not provided.

Control centres will use standard GP-led opportunistic recruitment and data collection methods. Patients will be identified as potentially eligible by their GP after checking their health record during the consultation. The GP will check for the exclusion criteria, and, if the patient is still eligible, they will provide them with information about the study. Upon patient consent, the GP will complete the CROM fields and the patient will be randomised to on-demand or continuous use of PPI following the randomisation design for the GORD study (i.e. block randomisation containing four blocks based on age and gender). The patient will receive a questionnaire to complete either at the primary care centre or at home. Patients will be followed up using paper-based questionnaires.
Primary outcome
The primary outcome measure is the proportion of eligible patients successfully recruited using the TRANSFoRm method compared to standard GP-lead opportunistic recruitment. A record of all identified, screened and successfully recruited patients will be kept using data from GP systems. The percentage of those recruited in the trial will be compared to identify whether TRANSFoRm yields a higher number of recruited patients compared to standard GP recruitment.

Secondary outcomes
Secondary outcomes will include the proportion of GORD cases recruited with complete baseline and follow-up data, as well as the proportion of those giving informed consent to participate but later withdrawing from the study. All electronic or paper-based CRFs completed by the recruited patients in each group will be reviewed, and retention data will be collected to examine whether there is a difference in the percentage of patients with complete data and the numbers of participants withdrawn or lost to follow up among the two arms.

Economic evaluation
A cost analysis will estimate the costs of recruitment using the TRANSFoRm system and the standard method. A similar approach was adopted in a previous study comparing recruitment methods across sites [12]. The analysis will focus on the direct costs incurred to the primary care centre during the implementation and operation phases. Patient and third party costs will not be included. Trial administration costs, including labour and material costs and personnel time spent will be identified and combined with recruitment data to model the average cost per site and enrolled participant. Non-recurring costs will spread out over 15 years and will be discounted at a 3.5% rate. If TRANSFoRm results in increased recruitment but is also more costly, the cost per additional participant will be estimated to assess whether this excess cost is acceptable.

Technology acceptance survey
User acceptance of the TRANSFoRm tools will be measured in a centrally coordinated technology acceptance survey. The Technology Acceptance Model (TAM) questionnaire is a validated instrument for collecting post hoc perceptions of a technology artefact segregated into two domains: usefulness and ease of use [13-15]. Data will be collected retrospectively through an electronically distributed questionnaire to all intervention arm participants.

User experience interviews
Clinician and patient experience with the TRANSFoRm tools will be assessed in follow-up, semi-structured, in-depth interviews with a purposive sample of interesting cases (i.e. GPs and patients with positive and negative experiences who demonstrated high/low usage patterns during the study). This interview study aims to assist interpretation of quantitative data generated by the main evaluation study by exploring: i) methods of recruitment and follow-up (e.g. web/mobile- vs. paper-based PROM); ii) reasons for any observed variations in recruitment performance across sites; iii) barriers and facilitators to successful recruitment; and iv) areas for improvements.

Sample size
We estimated the average number of eligible GORD patients per primary care centre to be at least 100 during the 16-week recruitment phase, based on a conservative GORD prevalence of 10% [16] and a list size of 2,000 patients. We conducted a binominal power calculation taking into account the variation in centre characteristics. This showed that 536 participants across 40 centres, 20 per arm, will give the study 90% power to detect a 15% increase in recruitment, from 20% to 35%, using a conservative 5% intra-cluster correlation coefficient, at 5% significance level. Modelling conducted for the clinical study suggests that this will offer excess power to detect a clinically relevant change in self-rated health scores (±0.25 Reflux Disease Questionnaire points) between treatment groups.

Randomisation, allocation and blinding
Primary care centres will be assigned to the TRANSFoRm or control arm on a 1:1 allocation ratio. The allocation sequence will be computer-generated using a within-country permuted random block design with blocks of two matched for list size, GORD prevalence, location, ratio of GORD appointments per week to list size and ratio of GPs to list size. The study is unblinded as it is impossible to blind primary care centres or investigators to the intervention. However, the allocation will not be shared with those involved in the data analysis to maintain objectivity and minimise bias.

Statistical methods
The percentage of patients recruited to the study for the intervention and control groups will be calculated using descriptive statistics with 95% confidence intervals. These will be presented separately for each site, country and overall. The proportion of eligible participants recruited will be compared between groups using logistic regression, adjusted for clustering by centre by using generalised estimating equations (CI 95%, P < .05). Between-group differences in recruitment rate will be analysed using chi-square tests. This method will be also applied to compare the percentage of participants with complete data and the percentage of
eligible patients who were recruited but later withdrew or lost to follow up.

Descriptive statistics will be used to outline the relative proportion of participants who were satisfied or dissatisfied with the TRANSFoRm tools as per item on the TAM questionnaire. Quantitative data will be analysed in STATA (v13) using an intention-to-treat approach.

Data from the user experience interviews will be audio-recorded, transcribed verbatim and analysed thematically using Ritchie and Spencer’s framework analysis approach [17].

The study has been designed and will be reported in CONSORT-compliant format [18].

Handling and storage of data

The study will be conducted according to good clinical practice standards. The handling of personal data will comply with the Personal Data Protection Act 2012 and local data protection regulations. Data collected from EHR systems and mobile/web applications using the TRANSFoRm system will be stored in a secure site hosted by Custodix (a private company specialising in data protection solutions in eHealth). TRANSFoRm has implemented technical measures to ensure that identifiable personal data is protected and that study data in the TRANSFoRm study system is protected by access authorisation and pseudonyms. Data for the control group will be transcribed from the paper-based forms via a web-based clinical data capture system hosted on a secure data repository at King’s College London. At the end of the study, all data will be securely transferred to Custodix to create the analysis dataset. This will only contain pseudonymised data. After analysis and reporting, data will be archived at the Karolinska Institute in Stockholm for 15 years.

Discussion

Recruitment failures in primary care are common due to the complexity of recruiting patients in this setting. To date, the most effective method for recruiting patients to primary care trials is opportunistic recruitment. This is performed manually using paper- or web-based case report forms and relies on busy GPs actively approaching potentially eligible patients in the consultation room and inviting them to take part. In an increasingly demanding healthcare system, such methods are highly time-consuming, and as a result, many studies fail to achieve their recruitment targets or to even recruit a single patient [1,19,20]. Recent advancements in information technology have enabled researchers, technologists and clinicians to collaborate with the aim to develop systems that can overcome these challenges and support effective recruitment. The TRANSFoRm system aims to transform patient recruitment and follow-up in primary care by automating the processes for identifying, recruiting and following up patients, potentially saving time for health professionals, which can be used instead in care delivery. The study described in this protocol will evaluate the effectiveness of TRANSFoRm in improving the efficiency, time and costs of recruitment and data collection. The study will provide an evidence base for eHealth-supported recruitment and follow-up in primary care. Participant recruitment is scheduled to commence in February 2015 and be completed by May 2015. The scheduled end of follow-up data collection is July 2015. Reporting of results is expected in October 2015.

The study design has been tailored to the objectives of the evaluation and the characteristics of the GORD study. The evaluation focuses on the socioeconomic aspects of the system. The main goal is to ensure that TRANSFoRm can improve the efficiency, time and costs of conducting clinical research in primary care. The evaluation strategy draws on valid and reliable methods which have been widely used in health informatics research to assess the effectiveness of eHealth interventions [21]. The study will use quantitative and qualitative data collection techniques that enable triangulation of findings adding to the internal validity of the study. It will recruit urban, suburban and rural primary care centres in five countries and will employ culturally diverse study participants increasing the sample representativeness and thus external validity.

The evaluation will include patients with GORD, and otherwise eligible for the study, for whom a single clinic appointment was made during the recruitment period. This measure guards against the possibility that participating centres embark on an active programme of recruitment of potential participants rather than, as instructed, relying on opportunistic presentation. Local EHR and appointment datasets will be used to validate this process. An in-depth audit will be undertaken of any centre where the appointment rate lies more than two standard deviations from the within-country mean. In all other centres, a random selection of appointments created for GORD patients during the recruitment period will be audited by an evaluation team member in liaison with a local collaborator.

The study has some weaknesses. The scope of the economic analysis is limited to the care centre level. This practically means that we cannot assess the costs and benefits for all stakeholders in the project. However, patients will be able to provide qualitative feedback on the impact of the TRANSFoRm tools in follow-up interviews and a TAM survey. Another limitation is that the study timeline is relatively short to evaluate the long-term effects of the intervention, despite being sufficient to recruit the required number of participants and collect data to explore the evaluation aims. Considering that technology adoption is a complex process [22,23], the time from implementation to evaluation is relatively short to assess the performance of the TRANSFoRm system.
The protocol provides a reproducible process for conducting a summative evaluation of the TRANSFoRm system based on the GORD clinical trial. The evaluation study focuses on assessing the effectiveness of TRANSFoRm-supported recruitment and follow-up in primary care research compared with standard GP-led opportunistic recruitment. The study should provide useful information about the use of information technology to improve the efficiency, time and costs of recruitment and follow-up in primary care and is expected to provide an evidence base for future eHealth-supported recruitment initiatives.

Acknowledgements
This project has received funding from the European Commission’s Seventh Framework Programme for research, technological development and demonstration under grant agreement number 247787. We would like to extend our gratitude to Ellen Wright from King’s College London, Peter Leysen from Imperial College London, and Hilde Bastiaens from the University of Antwerp, Karin Hek and Robert Wilson from Imperial College London, for the methodological advice. We are also extremely thankful to Ajay Gupta of the Medical University of Warsaw, Grzegorz Bliźniuk from the Medical University in Wroclaw, Agapi Śniuk-Lańczyk from the Centre for Health Information Systems in Warsaw, and Agapi Mastellos from the Centre for Family Medicine, Karolinska Institutet, for their contributions to the development and editing of the initial and subsequent drafts of the manuscript. LA conceived the clinical study and provided critical review of the protocol. LA, KH and ML participated in the design and helped to draft the manuscript. NM contributed to the design of the evaluation and drafted the manuscript.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
NM contributed to the design of the evaluation and drafted the manuscript. AA, KH and ML participated in the design and helped to draft the manuscript. VC and JC provided intellectual input to the design and drafting of the protocol. LA conceived the clinical study and provided critical review and editing of the initial and subsequent drafts of the manuscript. BD is the principal investigator of the study and participated in its conception, design and coordination. All authors read and approved the final manuscript.

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Published online: 03 February 2015

References
Appendix

C: TAM Participant survey
Evaluation of TRANSFoRm in the Gastro-Oesophageal Reflux Disease use case: technology acceptance survey

STUDY PARTICIPANT QUESTIONNAIRE SURVEY

What is this all about?

This survey is being conducted as part of a study evaluating the effectiveness of TRANSFoRm in recruiting patients in primary care studies and obtaining complete baseline and follow-up data. The survey looks at technology acceptance of the TRANSFoRm mobile and web applications that are used by the study participants to report Patient Reported Outcome Measures (PROM). You are being invited to complete this questionnaire because you have agreed to take part in the GORD study and have used the mobile and/or web application. The information you may provide will be used to inform the TRANSFoRm evaluation.

This study is being conducted by a team of researchers from leading Universities in Europe (for more information, visit http://transformproject.eu/TRANSFoRmproject.eu/Consortium.html) and is led by Professor Brendan Delaney (King’s College London).

What to do?

It is entirely up to you to decide whether you answer any or all of the questions in the questionnaire. If you decide to take part, please fill in the questionnaire and submit it online following the steps.

Any questions?

If you have any queries about this questionnaire and the study or if you would like to take the opportunity to give us more detailed feedback by taking part in one of the face-to-face interviews we organise, please contact Dr Anna Andreasson (email: anna.andreasson@ki.se) who will assist and provide you with any additional information you require.

Completion and return of this questionnaire will mean that you have consented for the research team to use your answers in reports or publications arising from the study.

All information you may give us will be treated in the strictest confidence.

This study has been approved by the <<enter name of Research Ethics Committee>> (Ref xxxxxx).
## Demographic Information

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</tr>
<tr>
<td>I have used the web app</td>
<td>Yes</td>
<td>No</td>
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## Section 1: Usefulness

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<tbody>
<tr>
<td></td>
<td>Extremely</td>
<td>Quite</td>
</tr>
<tr>
<td>1. Using the TRANSFoRm app(s) improves the quality of PROM reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Using the TRANSFoRm app(s) gives me greater control over the reporting of PROM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Using the TRANSFoRm app(s) enables me to report PROM more quickly</td>
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<tr>
<td>4. The TRANSFoRm app(s) supports critical aspects of the reporting process</td>
<td></td>
<td></td>
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<tr>
<td>5. The TRANSFoRm app(s) increases my productivity in reporting PROM</td>
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</tr>
<tr>
<td>6. The TRANSFoRm app(s) improves my performance in reporting PROM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. The TRANSFoRm app(s) allows me to accomplish more than would otherwise be possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. The TRANSFoRm app(s) enhances my effectiveness in reporting PROM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. The TRANSFoRm app(s) makes it easier to report PROM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Overall, I find the TRANSFoRm app(s) useful</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Section 2: Ease of use

<table>
<thead>
<tr>
<th>Statement</th>
<th>Likely</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extremely</td>
<td>Quite</td>
</tr>
<tr>
<td>1. I find it cumbersome to use the TRANSFoRm app(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Learning to operate the TRANSFoRm app(s) is easy for me</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Section 2: Ease of use

<table>
<thead>
<tr>
<th>questionnaire</th>
<th>Likely</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Interacting with the TRANSFoRm app(s) is often frustrating</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>4. I find it easy to get the TRANSFoRm app(s) to do what I want it to do</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>5. The TRANSFoRm app(s) is rigid and inflexible to interact with</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>6. It is easy for me to remember how to perform tasks using the TRANSFoRm app(s)</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>7. Interacting with the TRANSFoRm app(s) requires a lot of my mental effort</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>8. My interaction with the TRANSFoRm app(s) is easy for me to understand</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>9. I find it takes a lot of effort to become skilful at using the TRANSFoRm app(s)</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>10. Overall, I find the TRANSFoRm app(s) easy to use</td>
<td>✔️</td>
<td>❌</td>
</tr>
</tbody>
</table>

### Section 3: Attitudes towards use

<table>
<thead>
<tr>
<th>questionnaire</th>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Using the TRANSFoRm app(s) for reporting PROM is a good idea</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>2. The TRANSFoRm app(s) makes PROM reporting more interesting</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>3. Using the TRANSFoRm app(s) is fun</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>4. I like using the TRANSFoRm app(s)</td>
<td>✔️</td>
<td>❌</td>
</tr>
</tbody>
</table>

### Section 4: Intention to use

<table>
<thead>
<tr>
<th>questionnaire</th>
<th>Likely</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>If required in the future:</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>1. I intend to use the TRANSFoRm app(s) to report PROM</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>2. I predict I would use the TRANSFoRm app(s) to report PROM</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>3. I plan to use the TRANSFoRm app(s) to report PROM</td>
<td>✔️</td>
<td>❌</td>
</tr>
</tbody>
</table>