ORIGINAL ARTICLE

A priori consent within pragmatic randomised controlled trials: a web-based survey of statin use in primary care

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ABSTRACT

Background Clinical research methodology is evolving with the advent of pragmatic randomised controlled trials (PRCTs). Novel approaches for informed consent in PRCTs are needed.

Objective To explore public opinion about different ways of giving informed consent for PRCTs.

Design Web-based survey assessing acceptability of three PRCT consent scenarios for statin use.

Setting Community-based study.

Participants 678 (12%) adults responded to an open-access web-based survey.

Measurements Participant-rated acceptability of three different options for giving informed consent for a PRCT testing two commonly prescribed, effective treatments: statins for hyperlipidaemia. Option A was written informed consent given a priori for a specific study, with verbal confirmation of consent at time of randomisation. Option B was written informed, general consent a priori for multiple comparative effectiveness studies, with verbal confirmation for a specific study at time of randomisation. Option C was written informed consent for a specific study at time of randomisation.

Results Acceptability was higher for option A (475/529 (89.9%)) and B (441/487 (90.6%)) compared with C (339/481 (70.5%)). The estimates of differences in paired proportions were A versus C, 19.4% (95% CI 14.4 to 24.5), p<0.001; B versus C, 20.1% (95% CI 15.2 to 25.0), p<0.001.

Limitations The study design may have been subject to cognitive biases such as framing and anchoring effects. The anonymised web-based survey allowed no follow-up or verification for missing data. The sampling frame used an institutional database and social media and selection bias and halo effects may have been present. The 12.3% response rate may represent poor generalisability.

Conclusion The concept of giving a priori consent, with subsequent confirmation at time of randomisation in a PRCT, was more favourable than the traditional model of consent in a general-practice-based study of statin use.

INTRODUCTION

After the usual phases of drug research and development, new, approved medications become available for use in a general population. However, the broad patient groups who are actually prescribed these novel treatments may not resemble those studied in conventional preregistration randomised controlled trials (RCTs). Such generalisability of RCT findings to patients seen in primary care settings is an important management issue for general practitioners.[1] Furthermore, a contemporary systematic review of medications marketed between 2000 and 2010 reported that studies used as part of the approval process of new medications often have insufficient numbers of patients to reliably estimate long-term safety and efficacy outcomes.[2] Drug safety monitoring mechanisms exist for licensed medications, but far less resource is invested in studying the comparative efficacy and safety of medications already in use in general clinical populations.[3]

These issues have led to the concept of pragmatic randomised controlled trials (PRCTs). These are designed to allow the accumulation of large-scale and clinically representative data for comparative

studies within routine clinical practice. The use of electronic health records (EHRs) to identify potential participants, record consent, achieve enrolment and perform randomisation means that the administrative cost of a trial does not necessarily increase markedly with sample size. Embedding PRCTs within the healthcare provision framework has the potential to create a learning healthcare system (LHS) that informs best practice by randomising common, real-world treatment decisions, coupled with continuous audit and data collation.[4 5] Achieving informed consent is a critical barrier for LHS, and there is currently no widely accepted standard for this.[6 7]

Any research at the interface of primary care is inevitably hindered by logistic factors intrinsic to that environment such as time pressure, cost and data management. With these in mind, a PRCT, embedded into routine practice, needs a new strategy to ensure that adequate informed consent is obtained but also accounts for practical issues such as short time-windows between diagnosis and treatment and respecting clinician workload in primary care. A number of perspectives exist regards to appropriate informed consent in PRCTs. These include: that consent is not required for comparisons of two commonly used, efficacious medicines[8]; that the level of requirement for consent depends on context of the study or intervention[8 9]; and the absolutist argument that, if a patient is intentionally randomised to one of two treatments without consent, despite both being approved and commonly prescribed, this contravenes the physicians' duty to respect patient autonomy.[10] The most relevant perspective is likely that of patients themselves, with at least one study reporting patient preference for written consent over verbal consent for involvement in a PRCT.[11]

We propose a hybrid model as an alternative approach of obtaining written informed consent. This is where 'in principle' written consent to participate in a PRCT is obtained, indicating a general willingness to participate in a PRCT but before a particular diagnosis may have been made and enrolment considered and that consent is verbally confirmed at an enrolment visit, prior to actual randomisation. In this model, a group of patients is contacted directly by their general practitioner, with the full details of the specific PRCT. Those who are interested then contact the central study team to discuss the clinical trial. Potential trial participants subsequently return a form giving their written informed consent, in principle, to participate in the trial, should they require a prescription for the relevant diagnosis in the future. This information is integrated into that patient's EHR, and when the appropriate diagnosis is entered during a clinical consultation and a treatment about to be prescribed, consent is verbally confirmed and recorded within the EHR and randomisation occurs electronically. Giving a priori consent in principle to participate in more than one such PRCT, prior to diagnosis or need for treatment and enrolment in a specific PRCT, is a potential variation on this approach.

The aim of this study was to explore acceptability of a hybrid model for consent compared with a traditional consent process, in a group similar to those who might be recruited into a pragmatic trial in a primary care setting.

METHODS

A sample survey, collecting de-identified information and using an online questionnaire to record basic demographic information, attendance at primary care, previous experience as a clinical trial participant and opinions about three models of consent.

Participants and setting

The public survey link was sent to the Medical Research Institute of New Zealand (MRINZ) participant database, n=2288, using email and made available to members of the public who follow MRINZ on social media, n=3242 (as of October 2016). Informed consent for survey participation was assumed by submission of the questionnaire, as stated on the information provided as a preamble.

PRCT scenario and consent processes

A hypothetical study was described in the sample survey. The survey is shown in online supplementary appendix 1. In brief, the study scenario was for randomisation to one of two licensed statins in the event that a patient was considered by their primary care practitioner to require a statin as part of cardiovascular disease risk management. The participants were asked to rate each of three methods of consent as 'Acceptable' or 'Not acceptable'. The presentation of scenario order was fixed. The three models of consent were, as described in Box 1:

- Consent Model A: Prior specific consent in principle with verbal confirmation of consent at time of prescription.
- Consent Model B: Prior general consent in principle with verbal consent at the time of prescription.
- Consent Model C: Consent at the time of prescription.

The main estimates of interest were the proportions of respondents who nominated whether the specific scenarios were acceptable and whether these proportions were different.

Sample size

We planned to recruit a minimum of 400 participants so that the margin of error for estimation of a proportion, assuming a scenario had 80% agreement, was about plus or minus 4%.

Statistical analysis and data collection

The comparison of paired proportions for the scenarios was by generalised linear model for paired proportions using the SAS procedure 'CATMOD' and the p value by McNemar's exact test. Study data were collected and managed using REDCap electronic data capture tools hosted at MRINZ.[12]

Box 1 Three methods of consent

Consent Model A: Prior specific consent in principle with verbal consent at time of prescription
Patients are contacted by their general practitioner with information about a specific study that it is recruiting for. The study looks at the efficacy of two commonly prescribed treatments for a specific condition. Patients have the opportunity to contact the research team to discuss the trial and the information (up to 20 pages) they have been provided. If the patient agrees to participate in the study in the event that they require treatment for the relevant condition in the future, they return their signed consent to the central coordinating research team. At the prescription consult, the general practitioner confirms consent and randomises the participant to one of the two study medications. The prescription is collected from a pharmacist and routine follow-up continues, along with any study-specific contact from the research team, as outlined in the original study documentation received. If the patient does not participate, one of the two medications is prescribed as part of usual care.

Consent Model B: Prior general consent in principle with verbal consent at the time of prescription
Patients are contacted by their general practitioner with information that the surgery is involved in a research programme, with multiple subprojects comparing the effectiveness of commonly prescribed medications. Each study is described in detail (up to 20 pages) and if the patient is interested in participating in this type of research, they return a signed consent form to the coordinating research team. Details of subsequent studies will be made available as they arise. If a condition being studied is to be treated during a general practice consultation, consent is verbally confirmed and randomisation to one of the two study medications occurs. A prescription is collected from a pharmacist and follow-up takes place under routine care, along with any additional study-specific contact as detailed in the original patient information documents. If the patient does not participate, one of the two medications is prescribed as part of usual care.

Consent Model C: Consent at the time of prescription
During a routine consultation, treatment is planned for a diagnosis, which is the focus of a clinical trial at the general practice. There are two commonly prescribed medications and the patient would be randomised to one or the other. A participant information and consent form (up to 20 pages) is provided at the time of diagnosis and any immediate questions may be discussed with the general practitioner at that time. If the patient wishes to consent to the study, they sign the consent form and then are randomised to one of the two medications, which they collect from a pharmacist. Follow-up is routine with any additional study-specific contact from the research team detailed within the information. If more time is required to decide, no medication is prescribed and a further appointment is booked. If the patient does not participate, one of the two medications is prescribed as part of usual care.

Analyses used SAS V.9.4.

The study was reviewed and approved by Victoria University of Wellington, New Zealand, Human Ethics Committee; reference 22859.

RESULTS

Participant characteristics

A total of 678 responses were received between 25 July and 25 October 2016. This represents an overall response rate of 678/5530 (12.3%). In all, 465/678 (69%) of respondents completed the scenario acceptability questionnaires, of whom 236/678 (34.8%) respondents reported previously giving informed consent for a clinical trial and 229/678 (33.8%) respondents reported no prior experience in giving informed consent for a clinical trial. Respondents had a mean age of 53 and were predominantly female (65.2%), NZ European (85.3%), married (51.1%) and employed (68.8%). Mean (SD) general practice attendance per year among all respondents was 4.22 (4.6), and the mean (SD) number of current prescribed medications was 2.82 (2.64). Hypercholesterolemia was self-reported in 18%, with 58% of participants with this diagnosis reporting statin use. Participant characteristics are described in table 1.

Most participants who had previously given consent for participation in a clinical trial had done so more than once, primarily for altruistic reasons (table 2). About 60% of participants reported that they had read 100% of the consent form. While about two-thirds of participants considered that the amount of information in the consent form was 'just right', about one-third considered there was too much information.

Acceptability is summarised in table 3 and was higher for options A and B compared with option C, with rates of 89.9%, 90.6% and 70.6%, respectively (table 3). Previous participation in clinical trials or the prescription of statin therapy did not influence the responses for the acceptability of the scenarios. The paired difference between options A and B was −0.6% (95% CI −3.1 to 1.9), p=0.75, between options A and C was 19.4% (95% CI 14.4 to 24.5), p<0.001, and between options B and C was 20.1% (95% CI 15.2 to 25.0), p<0.001. The contingency tables are summarised in table 4.

DISCUSSION

PRCTs are an attractive alternative to traditional RCTs, with the potential to build a system that generates robust and informative data that could be quickly and efficiently translated into tangible clinical, epidemiological and economic health benefits. As part of an LHS, PRCTs have the benefit of engaging both patient and doctor in evidence-generating and evidenced-based healthcare. Advances in EHR technology mean that PRCTs are now technically feasible, but achieving informed consent in this setting has remained a challenge.

Table 1 Characteristics of participants

Variable	All responses n=678	Previous consent for clinical trial and scenario responses complete n=236	No previous consent for clinical trial and scenario responses complete n=235
Sex	n=615	n=235	n=235
Female	401 (65.2)	138 (58.7)	159 (67.7)
Ethnicity	n=613	n=233	n=235
NZ European	523 (85.3)	192 (82.4)	214 (91.4)
Māori	30 (4.9)	12 (5.2)	7 (3.0)
Pacific	6 (1.0)	3 (1.3)	1 (0.4)
Other	54 (8.8)	26 (11.2)	13 (5.6)
Marital status	n=609	n=235	n=232
Married	311 (51.1)	121 (51.5)	119 (51.3)
Widowed	12 (2.0)	6 (2.6)	3 (1.3)
Divorced	44 (7.2)	21 (8.9)	18 (7.8)
Separated	19 (3.1)	4 (1.7)	10 (4.3)
Never married	121 (19.9)	47 (20.0)	49 (21.1)
Living with partner	102 (16.7)	36 (15.3)	33 (14.2)
Employment status	n=603	n=234	n=231
Employed	415 (68.8)	169 (72.2)	148 (64.1)
Retired	124 (20.6)	48 (20.5)	50 (21.6)
Disabled and unable to work	14 (2.3)	3 (1.3)	7 (3.0)
Unemployed	50 (8.3)	14 (6.0)	26 (11.3)
High cholesterol	n=614	n=234	n=235
Yes	110 (17.9)	40 (17.1)	50 (21.3)
No	399 (65.0)	151 (64.5)	148 (63.0)
Not sure	105 (17.1)	43 (18.4)	37 (15.7)
Regular statin	n=108	n=39	n=49
Yes	63 (58.3)	25 (64.1)	29 (59.2)
No	41 (38.0)	14 (35.9)	16 (32.7)
Not sure	4 (3.7)	0 (0.0)	4 (8.2)

Table 2 Previous clinical trial experience

Variable	All responses n=678	Previous consent for clinical trial and scenario responses complete n=236	No previous consent for clinical trial and scenario responses complete n=235
Previous consent for clinical trial	n=612	n=236	n=235
Yes	292 (47.7)	236 (100.0)	0 (0.0)
No	320 (52.3)	0 (0.0)	235 (100.0)
Number of times consent given	n=281	n=227	
1	127 (45.2)	108 (47.6)	
2–3	122 (43.4)	94 (41.4)	
>3	32 (11.4)	25 (11.0)	
Amount of consent form read	n=288	n=235	
<50%	33 (11.5)	22 (9.4)	
>50% but <100%	57 (19.8)	48 (20.4)	
100%	159 (55.2)	136 (57.9)	
Unsure	39 (13.5)	29 (12.3)	
Amount of information in consent form	n=268	n=219	
Too little	5 (1.9)	3 (1.4)	
Just right	182 (67.9)	145 (66.2)	
Too much	81 (30.2)	71 (32.4)	
Reason for participating	n=287	n=233	
Altruism	166 (57.8)	135 (57.9)	
Personal benefit	49 (17.1)	37 (15.9)	
Financial	27 (9.4)	23 (9.9)	
Other	45 (15.7)	38 (16.3)	

Informed consent is standard practice for the conduct of clinical trials. However, aspects of informed consent can vary based on the clinical or research context, and one fixed model is unlikely to suit all scenarios.[7 13] Traditional consent models are not suited to conducting PRCTs that are embedded within routine primary care. Consequently, innovative approaches to achieving informed consent and a paradigm shift in how we think about consent in clinical trials is necessary. This requires a stepwise, exploratory approach to ensure all relevant opinions are considered and important ethical principles are protected. This survey explores the opinions of a group of participants who might be likely to be recruited into such a trial about a novel consent process with study information delivered and discussed before a clinical event that triggers potential enrolment.

The survey has shown strong approval for the system of a priori consent in principle, with around 90% considering this approach acceptable. This rating was maintained regardless of whether the informed consent related to a specific PRCT or multiple PRCTs that were being undertaken at the medical practice. In contrast, around 70% of participants considered the traditional consent model, where consent is obtained opportunistically at the point of diagnosis, acceptable. As a preliminary finding in the exploration of feasible consent for large-scale, community-based PRCTs, this is encouraging and perhaps indicative of an outdated ethical dogma of 'one size fits all', hindering progress in a promising methodology. The opinions were similar regardless of whether survey respondents had previous experience with giving informed consent or not.

There are theoretical strengths and weaknesses of the a priori and traditional models of informed consent. With a priori consent, participants have more time to consider the trial information provided to them. In many RCTs that use the traditional consent

Table 3 Scenario acceptability

Variable	All responses n=678	Previous consent for clinical trial and scenario responses complete n=236	No previous consent for clinical trial and scenario responses complete n=235
Scenario A acceptability	n=529	n=236	n=235
Yes	475 (89.8)	207 (87.7)	216 (91.9)
No	54 (10.2)	29 (12.3)	19 (8.1)
Scenario B acceptability	n=487	n=236	n=235
Yes	441 (90.6)	210 (89.0)	217 (92.3)
No	46 (9.4)	26 (11.0)	18 (7.7)
Scenario C acceptability	n=481	n=236	n=235
Yes	339 (70.5)	172 (72.9)	160 (68.1)
No	142 (29.5)	64 (27.1)	75 (31.9)

Table 4 Paired contingency tables for acceptability of consent for scenarios

	Consent A acceptable		Total
Consent B acceptable	Yes	No	
Yes	420	21	441/487 (90.6)
No	18	28	46/487 (9.5)
Total	438/487 (89.9)	49/487 (10.1)	487 (100)
	Consent A acceptable		**Total**
Consent C acceptable	Yes	No	
Yes	298	39	337/479 (70.4)
No	132	10	142/337 (29.7)
Total	430/479 (89.8)	49 (10.2)	479 (100)
	Consent B acceptable		**Total**
Consent C acceptable	Yes	No	
Yes	303	31	334/473 (70.6)
No	126	13	139/473 (29.4)
Total	429 (90.7)	44 (9.3)	473 (100)

model, participants may have to make decisions while unwell, and this, combined with time pressure, may preclude them adequately assessing the trial's merits. In contrast, the traditional consent model allows a decision to be made after the condition being studied has developed, rendering the concept of consenting for a trial more tangible. However, we would argue that, by requiring confirmation of the a priori consent at the time of enrolment, our approach overcomes this deficiency. The responses of participants who had previously provided informed consent as part of a clinical trial inform these considerations. Only around one-half reported that they had read 100% of the consent form, with around 10% having read less than 50%. Furthermore, around 30% considered that the amount of information in the consent form was 'too much'. Together, these findings suggest that the current requirements for detailed information within informed consent documentation may be excessive for the purpose intended, particularly when there may be some time pressure in providing consent.

This study has several important limitations. Framing biases may have influenced participant opinion as the necessary background information explained both the constraints on the traditional consent process in primary care and our intention to pilot the a priori approach. The a priori scenarios were placed first, and a degree of anchoring effect may resulted. Selection bias was also likely given the primary provision of the survey instrument to our institute database and by making it accessible via our research institute's social media profile. The open and anonymous nature of the study did not allow for verification of responses and made multiple entries possible, and a low 12.3% response rate may represent poor generalisability to a larger population. In addition, the a priori scenarios presented differed only in the amount of information (one vs multiple studies) that the patient was being asked to consider. A more practical approach to include would have been a scenario in which a defined group of patients with a particular diagnosis was contacted about the study, a priori consent in principle obtained and consent confirmed at the next prescription event where randomisation occurs. Such a study would be more suited to initially test the PRCT design as a priori consent is obtained from the patient who already has the diagnosis and for whom the study information will have greater clinical relevance.

The importance of an established, non-negotiable ethical standard such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to protect and inform research participants is irrefutable. Historical examples of research that lacked informed consent are both distressing and sobering.[14 15] These examples helped shape the understanding and application of medical ethics during the last century, in parallel with new treatments and improved health literacy. It is important that we do not preclude further advances in research methodology and consequent benefit to patients because we neglect to develop ethically sound and practical solutions to the problem of obtaining informed consent in PRCTs.

With the advent and increasing use of EHRs, the facility to run PRCTs and to develop an effective LHS clearly exists.[4] Recent attempts to conduct PRCTs have been hindered by governance and associated regulatory approval processes.[16] When considering the logistical hurdles, it is important to remember that the two major stakeholders in a community-based PRCT are the clinician and the patient. A key barrier

to clinician involvement in research is the additional time commitment it usually entails.[16] PRCTs can bring together patients who wish to be involved in research with clinicians who might otherwise have not been able to engage with clinical trials. Providing a research infrastructure that embeds informatics processes, such as randomisation and data collection, within routine clinical care minimises the time commitment for both doctor and patient. It is imperative that we find an acceptable framework for informed consent in PRCTs, now that other barriers—such as information technology—have been overcome.

Ensuring patient autonomy within the principles set by the ICH whereby '… a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate…' is perhaps the biggest challenge facing PRCTs.[17] However, we believe a hybrid approach such as a priori consent in principle, with a secondary confirmatory phase at the time of enrolment, has the potential to retain a fully informed consent process, while mitigating the logistical demand on the clinician at the primary care interface. The overwhelmingly positive response to the a priori scenarios, particularly when compared with the response to the traditional model of consent, suggests a public amenable to engaging in PRCTs that achieve consent in this way.

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