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Study protocol for a randomised controlled trial of enhanced informed consent compared to standard informed consent to improve patient understanding of early phase oncology clinical trials (CONSENT)

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ABSTRACT

Introduction Early phase cancer clinical trials have become increasingly complicated in terms of patient selection and trial procedures—this is reflected in the increasing length of participant information sheets (PIS). Informed consent for early phase clinical trials has been contentious due to the potential ethical issues associated with performing experimental research on a terminally ill population which has exhausted standard treatment options. Empirical studies have demonstrated significant gaps in patient understanding regarding the nature and intent of these trials. This study aims to test whether enhanced informed consent for patient education can improve patient scores on a validated questionnaire testing clinical trial comprehension.

Methods and analysis This is a randomised controlled trial that will allocate patients who are eligible to participate in one of four investigator-initiated clinical trials at the Royal Marsden Drug Development Unit to either a standard arm or an experimental arm, stratified by age and educational level. The standard arm will involve the full length trial PIS, followed by electronic or paper administration of the Quality of Informed Consent Questionnaire Parts A and B (QuIC-A and QuIC-B). The experimental arm will involve the full length trial PIS, exposure to a two-page study aid and 10 online educational videos, followed by administration of the QuIC-A and QuIC-B. The primary endpoint will be the difference (using a one-sided two-sample t-test) in the QuIC-A score, which measures objective understanding, between the standard and experimental arm. Accrual target is at least 17 patients per arm to detect an 8 point difference (80% power, alpha 0.05).

Ethics and dissemination Ethics approval was granted by the National Health Service Health Research Authority on 15 June 2020—IRAS Project ID 277065, Protocol Number CCR5165, REC Reference 20/EE/0155. Results will be disseminated via publication in a relevant journal.

Trial registration number NCT04407676; Pre-results.

Strengths and limitations of this study

- Innovative, prospective clinical trial examining informed consent for patients considering participation in currently open and active early phase clinical trials—enhanced validity and ability to translate results to clinical practice (as opposed to a simulated design).
- Multiple focus groups with patients with advanced cancer on early phase trials used to design the experimental interventions (two-page study aid and educational videos) to ensure they are as patient focused as possible.
- Truly informed consent is a topic of significant ethical and scientific importance in the current era of early phase clinical trials which are becoming an increasingly common part of the cancer journey for many patients, but for which there is a paucity of modern day research in the era of mandatory research biopsies, complex biomarker selected trial designs and increasing expectations of efficacy.
- Interventions are in English so results may not be directly applicable to patients from non-English speaking background.
- This study is running concurrently only with investigator-initiated early trials which as a group have slightly different characteristics to industry sponsored early phase clinical trials which may impact the generalisability of the results.

INTRODUCTION

Early phase oncology clinical trials are becoming increasingly complex with a rapidly increasing array of investigational agents, combinations of these agents and a variety of trial designs which incorporate the importance of personalised approaches.
Empirical research showing patients misunderstand early phase clinical trials

Multiple studies have shown that advanced cancer patients (ACP) misunderstand the nature and purpose of phase I oncology trials. Most recently, Hlubocky et al demonstrated through audiotaping clinical encounters between 101 ACPs and 29 oncologists, that ACPs had a poor understanding. Only 26% were able to recall the primary purpose of the trial as safety and only 7% were able to recall that there was a risk of major adverse effects such as organ damage. The study also demonstrated deficiencies in clinician communication, with only 40% of encounters containing a direct statement on the research purpose being to establish safety, toxicity and dosage. In 2010, a similar study of 17 oncologists and 52 patients in the UK showed that several key areas of information including prognosis were omitted from the clinical encounter. Joffe and colleagues also conducted a survey of trial participants (including phase I, II and III clinical trials) and investigators and showed significant deficits in understanding. Furthermore, in a survey of 95 patients on phase I trials, Pentz and colleagues demonstrated that 68.4% of patients had a therapeutic misconception by failing to answer two core questions correctly (1) ‘Is the research study mostly intending to help research and gain knowledge or mostly intending to help you as a person?’ (2) ‘Does the research study or your doctor decide the treatments?’ There was also a misunderstanding of the risk associated with participating in an early phase clinical trial and that they did not correctly grasp the key difference between individualised care and clinical research. In addition, there was a correlation between lower education and lower family incomes with therapeutic misconception. Overall, there is extensive empirical evidence to suggest that a significant proportion of ACPs considering early phase oncology clinical trials harbour misconceptions about the nature and design of these trials.

Participant information sheets are too long, too complex and fail to meet the information needs of patients

It has long been recognised that participant information sheets (PIS) or informed consent forms (ICF) are highly complex and lengthy across all the phases of oncology clinical trials. In 2007, Beardsley and colleagues showed that PIS were increasing in length and that an objective measure of informed consent (the Quality of Informed Consent Questionnaire Part A (QuIC-A)), understanding decreased as PIS’s increased in length. There have been no published studies on the PIS used in phase I studies specifically. However, in the era of combination trials, Bayesian adaptive design and seamless phase I/II designs, the PIS for phase I trials can be particularly complex and lengthy. While there is regulatory requirement for disclosure, these documents have ultimately become unwieldy, disliked by investigators and anecdotally, not read at all by some participants. This further magnifies the issues on therapeutic misconception that were highlighted earlier. We note that the Hastings Center has published a three-page phase I consent form with guidance on assessment of readability, but to the best of our knowledge this is not in widespread practice. Overall, in this era of increasingly sophisticated trial design, PIS are becoming lengthier and are becoming less useful as adjuncts to the informed consent process.

Paucity of interventional research to improve understanding

We performed a review of the literature looking at interventions that have been tested to improve participant comprehension of phase I trials which yielded two relevant studies. The first, a simulated teaching intervention to improve clinician confidence by Fallowfield et al showed that an intensive 8-hour educational intervention for clinicians involved in early phase trials improved their self-confidence along with patient simulator ratings of understanding. Second, Kass et al randomised 288 participants to receive either a 20-minute educational computer based presentation or a standard pamphlet on clinical trials and showed that they could improve patient understanding of trial purpose from 16% to 34% and also showed that there was no significant differences in likelihood of enrolment. We note that there have been multiple efforts directed towards empowering patients with cancer in later phase trials including audiovisual techniques such as multimedia presentations, question prompt lists and decision aids. Promisingly, sponsors are already taking steps towards improving their information sheets and there are already attempts to incorporate audiovisual materials and electronic assessment of patient understanding.

and the hope of fast tracked drug discovery. Informed consent for early phase oncology trials has always been a contentious area, and now it continues to be of relevance for the wider oncology community and the phase I trial community. A 2018 study demonstrated significant gaps in understanding of patients regarding the nature and intent of early phase oncology trials. There has been a longstanding debate in the medical oncology community about the nature of phase I trials and the ethics of allowing vulnerable patients to participate in clinical research where the primary purpose is to establish the safe dose. Opponents of the argument point to the need to understand both sides and that patients need to understand enough to consent, which is not necessarily full comprehension. The fact that this group of patients is hopeful, optimistic and desperate has been well characterised and no doubt plays a role in their ability to process information presented to them by the clinical research team. It is also important to recognise that consent for early phase trials deals with many of the same issues that are faced by clinicians considering consent in complex standard of care settings (eg, refusal of transfusion of blood components) with a focus on the key themes of preserving patient autonomy, protecting patient rights, ensuring jargon-free information and incorporating shared decision-making.
Justification for CONSENT

CONSENT will be a randomised controlled trial examining the effect of both a short (2 page), jargon-free, plain language participant information sheet and a suite of online educational videos, for participants considering consenting to an investigator-initiated trial (IIT) within the Royal Marsden Drug Development Unit. Early phase trials have dramatically changed over the last decade and there have been no interventional studies published in this area in this time and consequently this is a significant area of unmet need for both patients and investigators. This trial will use a validated measure of informed consent (Quality of Informed Consent—Part A). It is powered to test a statistical hypothesis of whether providing both a short summary PIS and a link to these online video modules will improve patient understanding as compared with a control group who are provided only the normal PIS. It will also examine the acceptability of the two interventions for patients. While the trial will employ a randomised design, it will ensure all participants including those randomised to the control group will be provided access to the enhanced consent materials prior to their actual consent visit to ensure fairness. This trial will also assess user acceptability and feasibility of the two interventions for patients.

METHODS AND ANALYSIS

Study aims

The primary aim of this study is:

- To establish whether the experimental arm can result in improved patients’ objective understanding (measured by the QuIC Part A) of early phase oncology clinical trials as compared with the standard PIS.

The secondary aims of this study are as follows:

- To establish whether the experimental intervention can result in improved subjective (QuIC Part B) patient understanding of clinical trials between the control group and the experimental group.
- To establish whether the experimental intervention can result in improved objective (QuIC Part A) and subjective patient understanding within the same patient as measured on the QuIC Part B.
- For the glioblastoma multiforme (GBM) cohort—to establish whether the experimental intervention can result in improved objective (QuIC Part A) and subjective patient understanding within the same patient as measured on the QuIC Part B.
- To confirm acceptability, uptake and utility of enhanced experimental interventions in this trial population.

Study materials

The first part of this enhanced consent will be a study aid (see online supplemental appendix 1) which contains the absolutely necessary information for patients—the design of this aid has been based on a qualitative study of patients on phase I trials and their informational needs. The top three priorities identified patients were

1. Will this trial work for me?
2. What are the side effects?
3. How often do I have to come? This will consist of an easy to understand flowchart.

The second part of this enhanced consent, based on the same data, will be an online link to 10 video modules (summary provided in table 1 and transcripts attached in online supplemental appendix 2) covering key areas of the consent. We asked about the key areas that need to be communicated, common areas of misunderstanding and preferred ways forward of improving patient understanding. We also used the feedback of the Royal Marsden Hospital Patient and Carer Research Review Panel to design these materials.

Study design and setting

Patient and public involvement

In 2019 we conducted a qualitative study of the key stakeholder groups in our early phase clinical trials unit in order to work out the design of the interventions used for this study. As part of that process we conducted two focus groups and gathered data on the key pieces of information that patients wished to know and ensured that these were incorporated into the design of the two-page study aid and also the content of the video. This protocol was presented to the Royal Marsden Hospital Patient Review Panel on multiple occasions and feedback was obtained about the nature of the study.

Endpoints

The primary endpoint of this study

- To determine the QuIC Part A scores following administration of a standard PIS alone, and compare it to the QuIC Part A score following administration of a standard PIS along with a study aid and a suite of online educational videos.

The secondary endpoints of this study are as follows:

- To determine the QuIC Part B scores following administration of a standard PIS alone, and compare it to the QuIC Part B score following administration of a standard PIS along with a study aid and a suite of online educational videos.
- To determine the changes in QuIC Part A and Part B scores before and after administration of enhanced consent materials in the control group only.
- GBM cohort—to determine the changes in QuIC Part A and Part B scores before and after administration of enhanced consent materials in patients recruited to the GBM cohort in the Ice-CAP study.
- To confirm the acceptability and utility of the study aid and educational videos with a user feedback survey (online supplemental appendix 3).
Inclusion/exclusion criteria

Inclusion criteria

► Eligible for an IIT within the drug development unit (RAF-MEK—NCT02407509, FRAME—NCT03875820, Ice-CAP—NCT03673787, ACE—NCT03177187).
► Patients with GBM eligible for Ice-CAP will not be randomised but assigned to a separate cohort.
► English is patient’s primary language.

Exclusion criteria

► Pre-existing visual, non-cancer related cognitive impairment or reading impairment.
► Patients who have already consented to a trial or have prior consent knowledge.

Study processes

This is a prospective, randomised trial running concurrently with our current standard of care for informed consent for our patients considering clinical trials—the design is summarised in figure 1. As per our normal standard operating procedure, patients are identified at a patient allocation meeting as potentially suitable for one of the four investigator-initiated clinical trials included in this study (RAF-MEK—NCT02407509, FRAME—NCT03875820, Ice-CAP—NCT03673787, ACE—NCT03177187). At this point, we will consider whether the particular patient would be suitable for CONSENT, and if suitable, the subinvestigator responsible for discussing the trial will also discuss whether the patient would be interested in participating in CONSENT. If the patient is interested then we will send the CONSENT PIS to the patient.

The study setting is the population of patients who are considered eligible for one of our investigator-initiated clinical trials at the Drug Development Unit, Royal Marsden Hospital, Sutton. Patients with GBM will be included in the study but will not be randomised. They will only be enrolled into the control arm and we will recruit up to 15 patients from the Ice-CAP trial. They are expected to have higher rates of baseline cognitive impairment and will be analysed separately.

As future IITs open in our unit, we will submit amendments in order to include them in CONSENT. At this point after the patient has received the CONSENT PIS, they will confirm during the follow-up phone call and can return the CONSENT ICF (online supplemental appendix 4) via email, post or during the next visit to hospital. Once they have consented, we will randomise the patient to either the control or experimental arm. The randomisation algorithm will be set up and managed by the Institute of Cancer Research Cancer Trials and Statistics Unit.

On the experimental arm, the patient will be provided the standard PIS, along with a link to the 10 online educational video modules and also a copy of the study aid for the IIT they have been allocated to. They will have at least 24 hours to review these materials, and they will then be asked to complete the demographic data collection form, the QuIC (Parts A and B) (please see17 for details on the...
instrument and scoring) and the feasibility questionnaire (online supplemental appendix 3). They have the option of completing the surveys and demographic data form (online supplemental appendix 5) via encrypted email or paper. They will then arrive for their consent visit as per standard of care.

On the control arm, patients will be provided the standard PIS, given at least 24 hours and then asked to complete the QuIC (Parts A and B) and demographic data form. Once this is completed, we will send the link to the online videos and also the study aid for their trial (as per the experimental arm). After at least 24 hours, the participants will then repeat the QuIC (Parts A and B) and the feasibility questionnaire. They will then arrive for their consent visit as per standard of care.

We will recruit a small cohort of patients with GBM from Ice-CAP (NCT03673787) to this study but they will not be included in the primary analysis due to the high prevalence of cognitive impairment in this group. This is a rare tumour that may stand to specifically benefit from enhanced consent and we thought it prudent to include these patients in a non-randomised fashion to obtain preliminary data on the efficacy and feasibility of enhanced consent in this group.

Statistical plan
Analysis population
The primary analysis in this trial will be comparison of the QuIC-A scores in the experimental group after exposure to the enhanced informed consent materials in addition to the standard PIS (standard of care) as compared with the control group after exposure to the standard PIS (standard of care). We will include all randomised patients for whom we have data on the initial QuIC-A (the primary endpoint). The patients recruited to the GBM cohort will not be included in the primary analysis.

Background on the QuIC-A instrument
The QuIC-A has been validated through rigorous testing as a tool for measuring the quality of informed consent in research participants. We performed testing within our unit and found it performed similar to the level expected in the literature. The average score on the QuIC-A among patients was 76.8/100 with a SD of 9.1.

We have consulted with the primary author of the QuIC and also looked at other literature using the QuIC Part A as a measure of informed consent and have found that a clinically meaningful score would be an improvement in score of at least 5 points.

We have also observed the statistical analysis for three other trials using the QuIC-A as a primary endpoint to test the effectiveness of an intervention to improve patient understanding of clinical trials. Tattersall et al. aimed to detect a difference of 5 points with the addition of a question prompt list, Hoffner et al. aimed to detect a difference of 5 points with an educational video about clinical trials and Spellecy et al. aimed to detect a difference of 4 points using an easy to read informed consent sheet.

In contrast to these studies, the experimental arm has two interventions we expect to be active—a two-page study aid, and also a suite of 10 jargon-free videos and we expect them both to have a significant impact on patient understanding of clinical trials and we expect this to be reflected in the QuIC Part A score to justify looking for a larger effect size (at least 8 points) between the experimental and control arms. Both interventions have been developed after an extensive qualitative analysis of our various stakeholder needs and requirements.

Randomisation
Once suitable patients are identified, consented and screened, they will be randomised in a stratified manner by two factors that we expect to impact on trial comprehension—age (over
65 or below) and educational level (university educated or otherwise). This will be performed with a minimisation approach and will be performed by the Institute of Cancer Research Clinical Trials Statistics Unit Randomisation Team—investigators will provide this team with the stratification factor information and will be informed of the allocation. Once informed, the study team will email the required interventions and questionnaires to participants. Participants and investigators will not be blinded once they have been randomised.

Analysis methods
We will use a one-sided two-sample t-test to determine whether there is a difference in the mean QuIC-A score between the control and experimental arm QuIC-A scores. We will use the same software to analyse the difference between the QuIC-B scores and also use the same method to compare the before and after QuIC-A and QuIC-B scores in the control arm using a paired t-test. If the distribution cannot be assumed to be normally distributed, a non-parametric unpaired and paired t-test using Wilcoxon rank-sum test and Wilcoxon signed-rank test, respectively, will be considered. The user feedback survey will be reported using descriptive statistics.

The primary and secondary endpoints of QuIC-A and QuIC-B will also be compared between the two arms using standard multiple linear regression models, with adjustment for the stratification factors of age and educational level. The model assumptions will be checked and if they do not hold, alternative modelling approaches will be explored as appropriate.

We will use Microsoft Excel (Office 365) or R to perform the analysis.

Sample size calculation for primary endpoint
We also understand the pragmatics of early phase clinical trials which have smaller numbers of patients and doing non-interventional studies on large groups of patients will not be feasible in this situation. We will aim to recruit at least 17 patients per arm, but we will recruit up to a maximum of 22 patients per arm. To detect an improvement of 8 points in the QuIC-A scores, we would require 17 patients per arm to give 80.6% power with a significance level (alpha) of 0.05 using a one-sided two-sample t-test (assuming SD of 9.1 for each group). If we recruit up to a maximum of 22 patients per arm, this will provide a higher power at 88.9% under the same test statistic and design parameters (difference of 8 points, one-sided alpha of 0.05 and SD of 9.1). We do not expect dropout from this study given the period of participation is short (between 24 hours after randomisation and up to a week), but if it does occur, we will recruit additional patients as appropriate.

Ethics and dissemination
Ethics
Ethics approval was granted by the National Health Service (NHS) Health Research Authority on 15 June 2020—IRAS Project ID 277065, Protocol Number CCR5165, REC Reference 20/EE/0155.

Safety considerations
Both the two-page study aid and the educational videos have been co-produced with patients so we have a minimal expectation of harm arising from participation in this trial. Anxiety due to the additional information may be possible and we will be formally studying this on the Brief User Feedback Survey (Item 1) but we will also escalate any concerns noted by investigators in this study to the principal and chief investigator so that they can be addressed quickly and safely.

Data handling and record keeping
We will permit trial related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and regulatory inspections and provide direct access to source data/documentation. The trial will be conducted within the standard operating procedures of both the Royal Marsden Hospital and the Drug Development Unit and the conduct of the trial will be regularly reviewed by both the principal investigator and the chief investigator.

The online data will be kept securely on a password protected database and participants will be provided with a secure link to access the survey data.

A key step will be the online questionnaires that need to be completed by study participants. Participants will complete this questionnaire online and then email it back to the secure clinical trial (NHS) email address, to which only the principal investigator or their specified delegate when they are on leave can access. The study participants will be informed that given their personal email addresses are not secure, there is a small risk that their personal data may be compromised when it is being sent to our email address. Patient demographic data will be stored on a password protected Microsoft Excel database.

Publication plan
Results will be disseminated via publication in a relevant journal.

DISCUSSION
To our knowledge, CONSENT is the first randomised controlled trial to test the efficacy of an intervention to improve patient comprehension of early phase clinical trials in cancer.

Informed consent is an extremely complex area to study due to the paucity of research, the vulnerability of this patient group and the heterogeneity of patient informational needs. The vast amount of literature documenting a lack of understanding juxtaposed with the stringent ethical demands of good clinical practice demands further efforts to actively seek to improve our consenting methods. Phase I trials, and the PIS accompanying them, are becoming more complex to understand.
and we are obliged to convey this information as simply as possible. We felt that a trial of simple and pragmatic interventions embedded within a real world setting will advance the field and provide information for both our unit and other phase I centres.

The study has multiple strengths. The intervention arm employs two novel interventions for patients considering early phase clinical trials—a two-page study aid and the set of 10 online educational videos. These have been created based on the results of an exhaustive qualitative analysis of all the key stakeholders in the informed consent process for early phase clinical trials including patients.18 Patient co-production is a particularly strong aspect of this study as patient input has played a pivotal role in the design of the experimental interventions and delivery of this trial. Second, this trial has a quantifiable primary endpoint which will objectively measure patient’s understanding of clinical trial. We have previously discussed the importance of measuring quality of informed consent19 and we are employing the QuIC-A as the primary endpoint for this study. Informed consent is a crucial component of good clinical practice and we believe measuring it, and particularly in studies such as these to examine the effectiveness of interventions is crucial.

Third, this trial is being conducted in a live setting running concurrently with patients considering on whether to participate in an early phase clinical trial. Performing a randomised study in this setting is additionally challenging but we believe this is the best way to isolate the effect of the interventions. It is crucial to note that all patients in CONSENT will receive the study specific ethics committee approved PIS up front so will not be disadvantaged by any ‘alternative’ information compared with those who do not take part in CONSENT. Additionally, to ensure equality within patients who take part in CONSENT, the standard arm will also receive the enhanced consent materials after completing the primary endpoint (QuIC-A). Given we anticipate this study will be completed electronically by the majority of the participants, we anticipate this trial will represent only a small additional burden for patients.

There are several limitations to this study. First, the early phase clinical trials included as part of this study are all investigator-initiated clinical trials—it is recognised in the literature and anecdotally that, on average, industry-sponsored studies will have longer PIS and more complicated schedules than IITs. Second, there is no baseline data on quality of informed consent as measured by the QuIC-A in the early phase clinical trials and this trial will be important in establishing this but it will make it difficult to benchmark. Additionally, the study is powered to detect a large difference in QuIC-A scores and it may miss a smaller effect size—this was a pragmatic decision based on the recruitment rate to early phase clinical trials and the complexity of managing recruitment to this study in parallel with recruitment to four clinical trials which have their own tempo of patient recruitment. Third, while the online and electronic nature of this study is a key benefit there remains a small risk of patient data being compromised. We have taken every effort to ensure our communications are encrypted via the NHS encrypted email system (nhs.net) but there remains a potential vulnerability in patient-sided technology —this is part of our consent sheet for this trial so patients are advised about this. Finally, we recognise that additional information may cause anxiety or distress for patients—we are recording this in our final survey as we seek to understand this but preliminary data from a separate project indicates that this is unlikely. We also provide the contact details for our clinical nurse specialists to all patients and we will provide support and clarification if required.

Results from CONSENT will help to inform the manner in which informed consent for early phase clinical trials is performed and will provide valuable information as to whether enhanced consent materials can impact on objective trial comprehension. We also hope that the focus on producing jargon-free and easy to understand information will be of relevance to other areas where consent is performed—for example, in standard of care settings in medicine. This is a key study in the broader effort to improve patient–clinician communication surrounding entry into early phase clinical trials, protect and enhance patient autonomy and ultimately better support patients with advanced cancer to make the decisions that are most congruent with their own values at the end of their life.

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Contributors AP performed the literature review and wrote the protocol under the supervision of JL, DK and FB. CY provided support with the statistical analysis and power calculations. RD, DM, BRB, SS and JK reviewed the protocol and provided feedback on each section. AM, UB and JDB reviewed the study design and provided feedback on the protocol. All authors read and approved the final manuscript. We will not be using the service of any professional writers. Once we have completed accrual for the primary endpoint, we will aim to publish the results in a relevant journal.

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Cellcentric, Daiichi, Eisai, Genentech/Roche, Genmab, GSK, Jansen, Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho and Vertex Pharmaceuticals. He is an employee of The ICR, which have received funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi, Genentech, Genmab, GSK, Jansen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi Aventis, Sierra Oncology, Taiho, Pfizer, Vertex, and which has a commercial interest in abiraterone, PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal income). He was named as an inventor, with no financial interest, for patent 8,222,438B2. He has been the chief investigator (CI)/principal investigator (PI) of many industry sponsored clinical trials. JDB is an NIH Senior Investigator. All related to this work: DK none declared; FB received fees for Advisory Boards for Roche, Novartis, Eisai, Pfizer and Eli Lilly. She has been the site PI/Ci for many industry sponsored clinical trials, all unrelated to this work. Friends of the Mater Foundation support her academic appointment at the University of Sydney and her supervision of this work. JL: research grant funding from Roche, Baselisa and Genmab, all unrelated to this work.

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**Author note** The study sponsor is the Royal Marsden Hospital and the contact email address is RDCCR@nhs.uk. The Royal Marsden Hospital Committee for Clinical Research provided initial review and feedback for this protocol—analysis and interpretation of data will be left to the study team.

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**REFERENCES**

Appendix 1: Example of a 2 page Study Aid

**Royal Marsden DDU Early Phase Clinical Trial Study Aid**

**Phase 1 Dose Expansion ICE-CAP (B1 prior IO, B2, B3 non resectable GBM)**

The complete trial participant information sheet (PIS) can be complex and this 2 page study aid is intended to help you understand your trial using simple jargon free language and clear diagrams. We have developed this summary based on feedback from patients to highlight information that you may find useful when making your decision to participate or not. Please use this study aid in conjunction with the online video educational modules we have provided you with.

1. **What is this trial testing?**

This trial is testing the combination of two anti-cancer drugs

<table>
<thead>
<tr>
<th>Atezolizumab (immune therapy)</th>
<th>Ipatasertib (IPA)</th>
</tr>
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<tbody>
<tr>
<td>an immunotherapy agent, approved for use in cancer care for the last four years, given as an injection through the veins (IV), designed to help your immune system recognise and slow down the growth of the cancer</td>
<td>A new/experimental oral targeted therapy drug, designed to target and reduce the activity of a overactive signal (Akt-PI3K) that drives cancer growth</td>
</tr>
</tbody>
</table>

2. **What type of clinical trial is this?**

This is a **Phase 1 dose expansion trial** and the main reason we are conducting it is to work out the side effect profile of this combination of drugs and whether they have any impact on cancer growth when used in humans. This combination has been through a dose finding stage where we worked out the safest dose to use. This trial will consist of procedures and treatments that are not standard for your type of and remember that these trials are designed primarily to understand these drugs to help future patients.

3. **Will it benefit me?**

We do not know. We allocate patients to a trial based on what has been observed in the lab (in glass dishes or animal models such as mice) or with patients who have tumours similar to you but this does not mean that you will necessarily benefit from this trial. It is possible that there will be no direct medical benefit from participating in this trial.

4. **What are the risks of participating in the trial?**

- We have an extensive understanding of the side effects of immunotherapy as it is a treatment that has been used in standard of care oncology for several years now. In the process of activating
your immune system, there can be autoimmune side effects and while these can be treated with steroids, sometimes these can be serious.

- Ipatasertib can cause high blood sugar and diarrhoea.
- For a full list of side effects please refer to page 8-10 of your trial information sheet.
- Given this is a new combination of drugs there may be unexpected side effects
- Risk to unborn children - if you are a woman and there is a chance you could be pregnant or a man and could father a child, you will need to adhere strictly to two forms of contraceptive measures during the study and for 6 months after the study -see pages 11 -12 of the trial PIS for more details.

5. What will this trial require of me?
- Phase 1 trials are time intensive and we will demand more of your time in terms of visits and procedures than ordinary treatment given in the clinic.

6. Do I have to go on this trial?
No - this is never the case, and there are always alternatives. For example, there is the option to focus on your quality of life– please discuss the risks and benefits of your various options with your doctors.

7. Who do I call if I am sick?
During the week, please contact Oak ward via Royal Marsden Hospital switch or the Clinical Nurse Specialist you met in clinic. On the weekends, please call the Macmillan Hotline who will direct your call to one of the Drug Development Unit Consultants, one of whom is on call 24 hours a day, 7 days a week. Safety is our key priority, and you should never hesitate to call us.

8. Will I be reimbursed for my travel?
Yes, please retain your fuel or public transport receipts for travel to and from the hospital and present them to the clerk on Oak ward. If you travel from afar, there may be capacity to reimburse staying near Sutton the night before.

9. Can I go on holidays during the trial?
We ask you to not schedule any holidays for the first two cycles – this an experiment and there may be unpredictable side effects that can only be managed by our specialist expertise. Our primary concern is your safety and we are not able to provide care if you are overseas or not reachable. Depending on the progress of your disease and how you tolerate the treatment we can discuss holidays from the third cycle on.
Appendix 2: Transcripts of Online Educational Videos

1. **What are early phase clinical trials?**

My name is Dr _____ and I am one of the consultant oncologists in the Drug Development Unit. Cancer is the leading cause of mortality in the developed world – unfortunately their remains an urgent need to develop more effective anti-cancer therapy with less side effects for almost all the major cancers. Scientists in a lab like this are working hard all the time – when they find a chemical that shows promising results in the lab, the next step will be to trial it in humans.

This is where we come in.

The first step is to work out if this new drug can be safely administered in humans and what the right dose to use is. We test these drugs in animal models but it is impossible to accurately predict how the drug will be tolerated in humans.

In the first part of a trial which you may be recruited in, called dose escalation, we start a dose where we do not expect to see any toxic side effects and then after a given time period passes after each patient at a particular dose, we slowly increase the dose until we start seeing side effects.

In the second part of the trial, called dose expansion, we have decided that a particular dose is tolerable and we are expanding the numbers of patients to start seeing if the drug has any anti-tumour efficacy and also continue to collect information about side effects.

Clinical trials have very specific inclusion and exclusion criteria, and also we only have a limited number of slots available at any particular time – it is understandable for you to be disappointed if there is no trial suitable for you.

2. **Will being in an early phase clinical trial shrink my tumour?**

My name is Dr _____ and I am one of the consultant oncologists in the Drug Development Unit. This is the most important question patients will have on their mind.

The answer is that we do not know. We may have an idea or a prediction based on the match between a particular trial and the characteristics of your tumour, but ultimately we do not know and this uncertainty is part of the research process. We make every effort to allocate you to a trial where we believe you will have the maximum chance of benefit. Saying this, it is crucial to remember that there is no proven benefit from trial participation.

This is perhaps the key difference for you to understand – there is a big difference between treatment offered with your referring oncologist which has been tried on thousands of patients and research trials where there has been a small number of patients who have been exposed to the treatments.

It is important for you to understand that the main purpose of an early phase trial is to establish the side effect profile and the correct dose of the drug to use – traditionally the question about whether the drug is effective is answered at later stages of development.

Historically response rates have ranged from 5 – 10% but your doctor will let you know if they expect the response rate to be or higher or lower in your particular situation during your consultation. Many patients ask how long a trial is, and the answer is that it depends on your response – for the majority of trials we usually wait 6 – 8 weeks to perform a scan and make a decision at that point about whether continuing on the trial is in your best interests.

3. **Will I get side effects by being on an early phase clinical trial?**
My name is Dr _____ and I am one of the consultant oncologists in the Drug Development Unit.

This is a vital area to understand however as side effects do occur on early phase trials and can be serious and potentially life threatening.

New cancer drugs may work brilliantly in the lab or a mouse, but unfortunately when given to humans, unexpected side effects can occur – while new agents are designed to be as targeted and precise as possible, it is unfortunately true that side effects are seen in early phase clinical trials.

Our primary concern is your safety and your safety comes first at every step of the way and is at the heart of the research protocols we design and create. Nevertheless, patients can suffer side effects and these can range from ones you may have experienced during previous therapies before such as nausea, diarrhoea, rash or numbness or tingling in the fingers and toes to more unexpected and concerning side effects.

It is important for you to understand that there is a distinct difference between treatment you have received before which has been tested in thousands of patients so doctors have a good understand of the side effect profile, to these research trials where the side effect profile is being worked out.

If you come to harm during our trials you can be assured that we will look after you and treat your side effects to the best of our ability.

4. **Do I have any other options? Am I missing out by not being on a Phase 1 trial?**

My name is _____ and I am one of the clinical nurse specialists in the Drug Development Unit.

Often patients coming to see us feel like they have no other options. That is never the case. We understand that patients coming to see us all have a diagnosis of an advanced cancer and that their time is precious – deciding to be on a Phase 1 trial means accepting the uncertainty of benefit, the uncertainty of risk and also spending time participating in research activities – this combination is right for some patients but not for all patients. You may have chemotherapy options available to you with your referring oncologist, you may have options at trial centres closer to home and you may take the option of best supportive care which means stopping anti cancer therapy and focussing on addressing any troublesome symptoms caused by your cancer such as pain or nausea.

5. **What is it like to be on an early phase trial?**

My name is _____ and I am one of the clinical nurse specialists in the Drug Development Unit.

Being part of an early phase clinical trial can represent hope for many patients coming to see us, and in some of our patients, we are able to control or shrink their cancer for a prolonged period of time which is our common goal. However, we like to explain to patients that being on an early phase trial is time consuming and at times, some patients can find it to be onerous.

Because these drugs are so new, we are extra careful and we have frequent clinic visits, usually once a week, to check on how you are going and to make sure you are not getting any side effects. We also have overnight admissions for many of our trials as we take regular blood samples to measure the level of the drug in your body. If you have an unexpected or serious side effect we will likely ask you to come to our unit so that we can review you, and if required, organise a hospital admission.
These visits are usually not so much of an issue for patients travelling a short distance to see us but definitely a consideration for patients who are travelling several hours to see us.

If you are working full time, it will likely interfere with your work schedule – if you are working part time, we will try to work around your schedule but you may still experience some interruptions. In addition, you will likely undergo one or more biopsies for the purposes of the trial and you will likely undergo more frequent imaging with CT or MRI than in your cancer care so far. Many of our trials with oral tablets may ask you to fast for one or two hours prior to having the tablet, and we will ask that you do not go on any holidays in the first two months of the trial – these are new drugs with unexpected side effects and we would not want you to be experiencing an adverse effect in a location where we are unable to review you. In summary, being on an early phase trial will change how you live your life during the time on your trial.

6. Why are biopsies part of many early phase trials and what is involved?

My name is Dr_____ and I am one of the consultant medical oncologists in the Drug Development Unit.

You may have had a biopsy during your cancer journey – most patients will have had one at the start of their journey when they were first diagnosed. A biopsy usually involves a trained doctor inserting a needle into an organ to collect a sample of cancer cells.

Many early phase clinical trials involve one or more biopsies – one prior to starting the clinical trial and one performed during the trial. Given these trials are early and we are uncertain of the benefit we are keen to look at whether the drug has impacted upon the tumour tissue in the way we thought it would. This information is vital for the development of the drug and to determine whether to use a higher dose or whether the drug is one that should be tested on larger numbers of patients.

There are two types of biopsies that we perform – superficial and deep. Superficial biopsies are performed of visible lumps on your skin while deep biopsies are performed in your abdomen of structures such as your liver. We will only request to perform a biopsy on you if it is a safe procedure to do so. The most common side effect of biopsies is pain and we have an extremely low rate of complications, but if a complication were to occur we would take the necessary steps to address it.

7. What types of imaging will I undergo?

My name is Dr_____ and I am one of the radiologists in the Drug Development Unit.

You will likely have had CT scans and other types of scans during your cancer journey – a key thing to understand about early phase trials is that we perform scanning more frequently and will likely perform some form of imaging with a CT, bone scans and/or MRI every 6 – 8 weeks. On rare occasions we do use PET scans as well. CT’s are performed within a matter of minutes and can be performed with or without contrast given through the veins. There is a small radiation exposure to CTs with each image, however if this is worrying you, you can discuss with the doctor what the risks mean for someone with advanced cancer. MRIs can take longer, up to 40 minutes and some patients find the machine claustrophobic and/or noisy. Please let us know if you have had any negative experiences and we will work to make the experience of imaging more comfortable.
8. **What will you do with my data?**

My name is _____ and I am one of the clinical governance specialists in the Drug Development Unit.

As part of your medical care, all your medical data is kept confidential between yourself and your treating doctor and their institution. In clinical research, your medical data provides valuable insight into how you are doing and helps the study team to monitor your safety. Often, a clinical trial is carried out at multiple hospitals in the UK and also, across the world. Your medical data that we collect here, will be de-identified, and unique study id is provided to your data. With this unique id, your medical data will be provided to study sponsors. This means that, your data will be anonymised. Sponsor will have access to your date of birth and your medical history and details of your consultations with us and results of any tests. This data is shared with them so that they can monitor the safety of the trial and to make decisions about the trials progress. If you have any questions about this aspect of the trial, please do not hesitate to ask the doctor and nurse you meet in our clinic.

9. **What is it really like #1? Does escalation**

   a. Explanation of trial they are on
   b. Personal experience of the trial
   c. Handling uncertainty
   d. Impact upon lifestyle
   e. Comments on quality of care received

10. **What is it really like #2? Dose expansion**

    a. Explanation of trial they are on
    b. Personal experience of the trial
    c. Handling uncertainty
    d. Impact upon lifestyle
    e. Comments on quality of care received
Appendix 3 - Brief User Feedback Survey

Unique Patient Identifier: _ _ _

1. Did you find the study aid distressing or uncomfortable?
   - Not at all distressing or uncomfortable
   - A little distressing or uncomfortable
   - Quite distressing or uncomfortable
   - Very distressing or uncomfortable

2. Did you find the study aid useful in helping you to understand the clinical trial offered to you?
   - Not at all useful
   - A little bit useful
   - Quite useful
   - Very useful

3. Please check the online videos you watched

<table>
<thead>
<tr>
<th>What is a Phase 1 trial?</th>
<th>What is it like being on an early phase clinical trial?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will the Phase 1 trial help me?</td>
<td>What types of imaging will I undergo?</td>
</tr>
<tr>
<td>What are the risks of a Phase 1 trial?</td>
<td>What happens to my data?</td>
</tr>
<tr>
<td>What are the alternatives to Phase 1 trial participation?</td>
<td>Patient perspective of a dose expansion trial</td>
</tr>
<tr>
<td>What are biopsies and why are they part of trials?</td>
<td>Patient perspective of a dose escalation trial</td>
</tr>
</tbody>
</table>

4. Did you find the online video educational modules distressing or uncomfortable?
   - Not at all distressing or uncomfortable
   - A little distressing or uncomfortable
   - Quite distressing or uncomfortable
   - Very distressing or uncomfortable

5. Did you find the online video modules useful in helping you to understand clinical trials?
   - Not at all useful
   - A little bit useful
   - Quite useful
   - Very useful

6. Please provide any comments about your experience of the enhanced consent materials
7. Did the extra information change your decision to participate in the trial? Yes/No
Appendix 4 – CONSENT PIS for Participants in Randomised Cohort

The ROYAL MARSDEN
NHS Foundation Trust

Drug Development Unit
Downs Road, Sutton
SM2 5PT 020 8642 6011

Participant Information Sheet

CONSENT - A Randomised Controlled Trial of Enhanced Informed Consent Compared to Standard Informed Consent To Improve Patient Understanding of Early Phase Oncology Clinical Trials

1. Invitation

We would like to invite you to take part in this research study – please take the time to review this information sheet and if you have any further questions, the study doctor or nurse will be able to discuss this with you.

2. What is the purpose of the study?

We would like to see if we can help patients better understand early phase clinical trials with a 2 page study aid and online video educational modules. Trial participant information sheets can often be over 15 pages and we know some patients have trouble reading through so much information. We also know that our trials are complex so we have designed a set of educational videos which are short and easy to understand.

3. What have I been invited to take part in the study?

You have been invited to take part as we have allocated you to a trial and sent you the trial information sheet. Participating in this information trial is optional but if you do choose to participate it would run at the same time you have to consent for the anti-cancer trial.

4. Do I have to take part?

No. Your decision to take part in this trial will not impact on your ability to participate in the anti-cancer trial in any way.

5. What will happen during the study?

If you elect to take part, you will receive standard informed consent information or additional material we have developed (videos and a 2 page study aid). This allocation will be done by chance (randomly) so that there are 2 equal groups we can compare. In the experimental group you will receive the standard anti-cancer trial information sheet, but will also receive a link to the online educational videos and the summary 2 page anti-cancer trial information sheet (2 pages). You will then be asked to complete two online questionnaires. In the control group, you will receive the standard anti-cancer trial information sheet, then receive a link to complete an online questionnaire. You will then receive the links to the online educational videos and a summary 2 page anti-cancer trial information sheet. You will then be asked to complete the first online questionnaire again, and also a second one.

6. What are the possible side effects?

You may find the additional information on early phase trials distressing or confusing – if this occurs, please contact your Phase 1 clinical nurse specialist or the study doctor and we will address your concerns. The trial uses online questionnaires and surveys – we will ask for basic demographic details to be entered and sent to us. While our email address is secure, we cannot guarantee the security of your method of connecting to the internet so there is a possibility your data may be compromised when being sent to us. If this is a concern for you, please contact us and we can discuss alternative options.
7. What are the possible benefits of taking part?

You may gain a better understanding of early phase clinical trials and the nature, purpose, risks and benefits of participating in a trial. It may assist you to make an informed decision, in line with your values, about whether you wish to participate in a trial.

8. Will my taking part in the study be kept confidential?

Your study data and questionnaire responses will be kept confidential but may be looked by regulatory authorities to ensure the trial is being conducted safely. The information will be collected and stored by the ICR for at least 25 years after the clinical trial has closed.

9. How will we use information about you?

We will need to use information from your responses to the questionnaires for this research project. This information will include your
- Initials and DOB
- RMH ID number
- Contact details

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

10. What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won’t be able to let you see or change the data we hold about you.

11. Where can you find out more about how your information is used?

You can find out more about how we use your information
- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to informed.consent@nhs.net or
- by ringing us on 0207 352 8171 and requesting to speak to the Royal Marsden Data Protection Officer

12. Involvement of GP/family practitioner

We will send your GP a letter to tell them you are taking part in this clinical trial.

13. Who is organising this study?

The study is being organised and sponsored by the Royal Marsden Hospital.

14. Who has reviewed the study?

All research in the National Health Service (NHS) is looked at by an independent group of people called a Research Ethics Committee to protect your safety, wellbeing, rights and dignity.

15. Further information and contact details

If you have any questions or concerns please contact Chief Investigator – Dr Juanita Lopez, Contact Number – 020 8661 3539.

Thank you for taking the time to read this information sheet
Appendix 5 – Demographic Data Collection Form

Demographic Data Collection Form

Thank you for participating in this trial. For this trial, we will collect the below information to help us understand the results.

<table>
<thead>
<tr>
<th>Unique Patient Identifier</th>
<th>_ _ _</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>18 – 24 □ 25 – 34 □ 35 – 44 □ 45 – 54 □ 55 – 64 □ 65 – 74 □ 75 – 84 □</td>
</tr>
<tr>
<td>Gender</td>
<td>Male □ Female □</td>
</tr>
<tr>
<td>Race</td>
<td>White □ Asian/Asian British □ Black □ Other ethnic group/mixed □</td>
</tr>
<tr>
<td>Highest educational level attained</td>
<td>Graduate degree (eg. PhD) □ Undergraduate degree (eg. Bachelors) □ Secondary school □ Primary school □</td>
</tr>
<tr>
<td>Do you have a support person who is involved in your medical care?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Is English the main language you speak at home?</td>
<td>Yes □ No □</td>
</tr>
</tbody>
</table>