Assessing the unmet needs of patients with advanced cancer treated by biological and precision therapies: protocol for TARGET, a mixed methods study

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ABSTRACT

Introduction Biological and precision therapies are increasingly used in cancer treatment. Although they may improve survival, they are also associated with various—and unique—adverse effects, which can be long lasting. Little is known about the experiences of people treated with these therapies. Moreover, their supportive care needs have not been fully explored. Consequently, it is unclear whether existing instruments adequately capture the unmet needs of these patients. The TARGET study seeks to address these evidence gaps by exploring the needs of people treated with these therapies with the aim of developing an unmet needs assessment instrument for patients on biological and precision therapies.

Methods and analysis The TARGET study will adopt a multi-methods design involving four Workstreams (1) a systematic review to identify, describe and assess existing unmet needs instruments in advanced cancer; (2) qualitative interviews with patients on biological and precision therapies, and their healthcare professionals, to explore experiences and care needs; (3) development and piloting of a new (or adapted) unmet needs questionnaire (based on the findings of Workstream 1 and Workstream 2) designed to capture the supportive care needs of these patients; and finally, (4) a large-scale patient survey using the new (or modified) questionnaire to determine (a) the psychometric properties of the questionnaire, and (b) the prevalence of unmet needs in these patients. Based on the broad activity of biological and precision therapies, the following cancers will be included: breast, lung, ovarian, colorectal, renal and malignant melanoma.

Ethics and dissemination This study was approved by National Health Service (NHS) Health Research Authority Northeast Tyne and Wear South Research Ethics Committee (REC ref: 21/NE/0028). Dissemination of the research findings will take several formats to reach different audiences, including patients, healthcare professionals and researchers.

INTRODUCTION

Survival continues to improve for many types of cancers. This is largely due to the promotion of early detection and advances in treatment approaches. A particular success has been the development of biological and precision therapies. These novel anti-cancer therapies have transformed the prospects for patients with advanced disease, where the aim of treatment is to generally prolong and improve the quality of life rather than to cure disease. While traditional cytotoxic chemotherapy is preferentially taken up by rapidly proliferating cells in the body, including normal and cancerous tissues, biological and precision therapies are more selective. Indeed, they interfere with specific cellular pathways that support carcinogenesis, including uncontrolled growth factor signalling, angiogenesis and evasion of the immune system. The availability and usage of these novel therapies is increasing exponentially, with over 250 treatments licenced to treat various cancers primarily in the

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This project is a sequential mixed methods study about people with cancer who are taking, or have taken, biological or precision therapies.

⇒ This project follows a rigorous methodological approach of conducting a systematic review and qualitative interviews to develop a questionnaire to assess unmet supportive care needs in these patients.

⇒ Current unmet needs questionnaires were developed before biological and precision therapies were commonly used and may not be appropriate for this patient group.

⇒ The unmet needs questionnaire will be piloted then surveyed with existing patients.

⇒ As the survey will be self-reported and anonymous, there will be limited opportunity to link with clinical data.
metastatic setting; this number is set to further increase in the future.

In the initial developmental stages of biological and precision therapy, it was anticipated that the profile to potentially cause adverse effects would be minor. This was considered a major advantage compared with traditional cytotoxic chemotherapy where adverse effects are common and, sometimes, severe enough to warrant dose reduction and treatment discontinuation. However, when biological and precision therapies are used clinically, it is apparent that they do cause adverse effects\textsuperscript{6} that potentially impact on the patient experience. For example, cardiac dysfunction, skin rashes, hypertension, blood clotting problems, mood disturbances, hepatitis and gastrointestinal disturbances have been associated with the use of biological and precision therapies. In the majority of cases, these adverse effects differ from those associated with traditional cytotoxic chemotherapy. Another important consideration is that of treatment duration: an important consideration is that of treatment duration; biological and precision therapies are often given for prolonged periods of time,\textsuperscript{6,10,11} meaning the adverse effects associated with their use may also be prolonged. There is, therefore, potential for the patient experience to be very different when comparing these biological and precision therapies to traditional cytotoxic chemotherapy. However, unlike traditional chemotherapy,\textsuperscript{14-18} there is limited literature exploring the experiences of people treated with biological and precision therapies, and the few studies that do exist have mainly focused on the use of tyrosine kinase inhibitors in the treatment of chronic myeloid leukaemia, which have now been available for almost two decades.\textsuperscript{19-21}

Supportive care is defined as care ‘that helps a person with cancer and their family cope with cancer and its associated treatment, from diagnosis through to treatment and cure, continuing illness or death, and bereavement’. Supportive care needs in cancer can be wide ranging and context bound,\textsuperscript{22,23} including physical effects of cancer and treatment;\textsuperscript{23} psychological effects, such as depression and anxiety; and information based, such as navigating the health system. Unmet supportive care needs—when individuals would like support, care or help but do not receive it—have been a major focus in cancer survivorship research over the past decade. This work has established that many patients/survivors with cancer have multiple supportive care needs and, in most healthcare systems, these needs go unmet.\textsuperscript{22,23}

Despite the rapid increase in the use of biological and precision therapies, the unmet needs of people receiving these therapies has not been fully explored. Given the differences between these novel anti-cancer therapies and the more conventional forms of cancer treatment, it cannot be assumed that the supportive care needs of patients will be the same. Differences in needs potentially include: challenges associated with treatment adherence and medication management; managing chronic adverse effects of treatment; and information needs and understanding in relation to the new treatments. A further evidence gap is around the instruments used to measure unmet needs, of which there are many.\textsuperscript{24} It is not clear whether these existing instruments adequately capture the specific needs of the patients being treated with these novel anti-cancer treatments.

The TARGET study aims to generate new knowledge and understanding of the experiences and supportive care needs of people with cancer who are taking, or who have taken, biological and precision therapies. We will develop a questionnaire for assessing unmet needs and determine the psychometric properties. We will estimate what proportion of patients using biological and precision therapies have unmet needs, identify the types of unmet needs most commonly experienced and identify which patient subgroups (eg, socio-economic, clinical) are most likely to experience these. Our findings will determine the potential need for additional resources and/or service developments to support the growing population of patients with cancer who receive biological and precision therapies.

AIMS AND OBJECTIVES

Aim

The TARGET study aims to assess the experiences and supportive care needs of patients with cancer treated with biological and precision therapies. With these insights, we will develop an unmet needs questionnaire to specifically capture the unmet needs for people receiving biological and precision therapies.

Objectives

1. To conduct a systematic review of existing unmet needs instruments in advanced cancer (workstream 1 (WS1)).
2. To explore, for patients treated with these therapies, and healthcare professionals treating patients, experiences and supportive care needs (met and unmet) (workstream 2 (WS2)).
3. To develop (or adapt) and pilot an unmet needs questionnaire for use in patients treated with biological and precision therapies (workstream 3 (WS3)).
4. To determine the psychometric properties of the new (modified) questionnaire and document prevalence and predictors of unmet needs among patients receiving biological and precision therapies (workstream 4 (WS4)).

METHODS AND ANALYSIS

This study will adopt a multi-methods design over four WSs (figure 1).

WS1: systematic review (months 1–9)

This WS (which has now been completed) involved a systematic review which aimed to (1) identify what instruments are available to measure unmet needs in adults with advanced cancer and (2) assess instrument development, content and quality, in terms of clinimetric
properties. The systematic review has been completed, and the results reported elsewhere.²⁵ In summary, the search identified 24 instruments, none of which specifically focused on patients using biological and precision therapies. Instruments had variable content and were mapped to different dimensions of unmet need (physical, psychological, information, social, activities of daily living, healthcare, spiritual, sexual, economic, autonomy and role). In addition, the methodological quality of the instruments, as assessed by the consensus-based standards for the selection of health measurement instruments (COSMIN) guidelines,²⁶ was variable. The findings from the systematic review will support the selection of an existing needs assessment questionnaire to develop and adapt, specific to the needs of patients using biological and precision therapies (WS3).

WS2: qualitative interviews (months 9–18)
Semi-structured interviews will be conducted to explore patients’ and healthcare professionals’ experiences of biological and precision therapies and patients’ supportive care needs. An interview schedule will inform the interviews and will cover a number of topics including views and experiences of biological and precision therapies (eg, what/if any side effects are experienced, how any side effects are managed; availability of information; concerns about treatment effectiveness; challenges of managing the treatment schedule), the availability and use of supportive care services/resources (eg, have the accessed centres/groups) and any areas where patients’ support needs may not be fully met. The schedule will be used flexibly, enabling participants to answer freely and allowing the interviewer to probe based on the responses given.²⁷ Approximately 30 professionals and 30 patients will be recruited; this is likely to be sufficient to reach reasonable data saturation.²⁸ Interviews will be transcribed verbatim, with analysis conducted in parallel with recruitment. This will allow for any new or unexpected topics which emerge in earlier interviews to be added to the interview schedule and explored in subsequent interviews. An inductive thematic analysis²⁹ will be conducted, allowing the generation of themes derived from the data. This approach will be employed in combination with a framework analysis,³⁰ with the 11 domains of unmet needs identified from WS1 informing the analytical framework. The findings from the qualitative interviews (WS2) will support the development of a needs assessment questionnaire (WS3), by revealing what areas of need both patients and professionals report in relation to biological and precision therapies. With this data, we can construct questions of high relevance to this patient group.

Recruitment for WS2
Both patients and healthcare professionals will be primarily recruited through UK NHS Hospital Trusts. Recruitment for professionals will be open to all those involved in the hospital care of patients receiving biological and precision therapies for the eligible cancers. Inclusion includes (but is not restricted to): consultant oncologists, registrars, cancer specialist nurses, palliative medicine consultants, healthcare assistants, psychologists, hospital pharmacists and any other relevant healthcare professionals. For healthcare professionals, the purposive sampling strata will be cancer site and discipline. Clinical collaborators will provide contact information to the research team of eligible healthcare professionals for the researchers to contact directly, or the researchers will...
provide the study information to research sites, so study information can be distributed directly.

For patient recruitment, clinical collaborators will (1) identify eligible patients from clinic lists and provide study information (face-to-face at a clinic visit or by post) or (2) identify eligible patients from pharmacy records and provide study information (face-to-face at a clinic visit or by post). Patients who are interested in taking part in the study will consent for their preferred method of contact to be passed onto the research team or they will contact the researchers directly who will then schedule an interview.

**WS3: questionnaire development: development, consent validity and pilot testing (months 18–27)**

Based on the findings from WS1 and WS2, and informed by international guidance in this area (COSMIN), an unmet needs assessment questionnaire for use in patients being treated with biological and precision therapies will be developed and piloted. Informed by the findings from WS1, consideration will be given to the feasibility of adapting an existing questionnaire identified in WS1 or developing a new questionnaire. Once the pilot instrument has been designed, both our patient PPI group and healthcare professionals will be approached to review the draft questionnaire against criteria for good content validity. After group discussions have occurred and any required revisions made, cognitive interviews will be conducted with patients with cancer to pre-test it. Participants will be invited to ‘talk aloud’ as they complete the questionnaire, with verbal probing used to clarify any problems or issues. An iterative approach to pre-testing will be used: first, several ‘rounds’ of testing with small groups of patients (n=3–5) will be undertaken; second, revisions and refinement (using a systematic approach to identify problems and changes needed) will be undertaken; and third, the revised version of the questionnaire will be further tested with patients. This approach will enable a better understanding of not only how people interpret the questions and response options but also the answers and their opinions on the questions being asked; it will help ensure content validity (eg, are the included items relevant to the target population). Recruitment will cease once no new issues are identified. The questionnaire will then be piloted with approximately 50 patients, who will be asked to complete it twice, with a 2-week interval, for test–retest reliability and to identify any areas of the questionnaire where final amendments should be made. The questionnaire will be designed for self-completion. It will be piloted with approximately 50 patients to identify any areas where final amendments should be made. These 50 patients will also be asked to complete the questionnaire a second time, after a 2-week interval, to enable test–retest reliability to be assessed. The finalised questionnaire will be used in the WS4 survey. As the questionnaire is anonymous, we will not be privy to any personal or clinical changes which may impact the results. Thus, a 2-week interval has been selected to minimise the chances of this. The finalised questionnaire will be used in the WS4 survey.

**Recruitment to WS3**

Recruitment will follow the same approach as WS2. In addition, any participant from WS1 who expressed interest to take part in further WSs will be invited to do so. In summary, clinical collaborators will identify eligible patients from clinic lists or from pharmacy records, provide study information about the study either face-to-face at a clinic visit, or by post, and invite them to participate. Face-to-face interaction will be the exchange of study information only; the questionnaire is designed for self-completion. For the pilot testing, patients will complete and return the survey (An information sheet will be provided with the survey, including that the survey is voluntary. Consent will be assumed through filling in and returning the survey.). Patients will be provided with both a paper survey and a link to complete electronically if preferred.

**WS4: survey of the new questionnaire among patients using biological and precision therapies (months 27–36)**

Using the new questionnaire, the unmet needs of patients with cancer with experience of using biological and precision therapies will be surveyed. The survey data will also be used to assess the psychometric properties of the new instrument. Based on an assumed prevalence of unmet supportive care needs of 40%),34 368 participants are required to estimate this with a 95% CI and 5% margin of error. Thus, an aim of 400 participants to survey with the new questionnaire has been set. Conservatively assuming a 50% response rate, 800 patients will be invited to this WS to ensure the target is met.

For the psychometric properties analysis, floor and ceiling effects, as well as the levels and patterns of missingness will be examined; exploratory or confirmatory factor analysis will be undertaken as appropriate (depending on whether or not the new questionnaire is linked to an existing ‘base’ questionnaire). The following will also be assessed: subscale/domain multitrait scaling and reliability using item-total correlations and Cronbach’s alpha; known group validity, by comparing responses between subgroups expected to have different needs; and discriminant validity versus the FACT-G and EQ-5D-5L. The primary outcome for the unmet needs analysis will be the proportion of patients with at least one unmet need, while secondary outcomes will include the number of unmet needs and proportions with each type/domain of unmet need. Outcomes will be compared between patient groups using univariable parametric and non-parametric methods, as appropriate. Socio-demographic (characteristics of a population, for example, age), social circumstance (markers of social status of a population, for example, who they reside with or educational level) and clinical factors (for example, current treatment) associated with primary and secondary outcomes and associations between unmet needs and health-related quality of life will be assessed.
of life will be determined using multivariable logistic or linear regression, as appropriate.

Recruitment to WS4
Recruitment will use the same processes as WS2 and WS3. Patients will be provided both paper and electronic versions of the survey and will be able to complete whichever one they prefer (An information sheet will be provided with the survey, including that the survey is voluntary. Consent will be assumed through filling in and returning the survey.).

Supplementary recruitment methods (if required)
The COVID-19 pandemic has created an unprecedented demand on health services (such as COVID-19 absences, research staff redeployed to wards, hospitals at capacity) and, consequently, has severely impacted the ability of hospital trusts and clinicians to participate in (non-COVID-19 related) research. Thus, supplementary recruitment methods will be adopted if required. This may include utilising social media and distributing the study information through charity patient networks, enabling participant self-referral to the researchers (WS2 only).

Eligible therapies and cancers
There is no universal definition of biological and precision therapy. For the purposes of this study, both biological and precision therapies\(^4\) as well as immunotherapies will be included. There will be no restriction to line of treatment (ie, whether the biological/precision medicine is first-line, second-line treatment) or whether treatment is being issued as part of a trial. Patients can also have had other treatments (such as, surgery, chemotherapy and radiotherapy), providing they are not receiving them at the time of recruitment (see table 1). To participate in the study, patients must have: advanced or metastatic cancer of the following types: lung, breast (Selective Estrogen Receptor Modulators (eg, tamoxifen) and aromatase inhibitors have been excluded due to an extensive evidence base already existing on women’s experiences of taking these drugs.) (female), colorectal, ovarian, renal or malignant melanoma. These cancers were selected based on (1) the recommended use of biological and precision therapies in their clinical management; (2) the different classes of biological and precision therapies recommended for use; (3) varying age of diagnosis and (4) varying socioeconomic distribution of cases (see table 1). This approach will help ensure our sampling captures the diverse experiences and varying needs of people using biological and precision therapies. It is important that one cancer type, or patient demographic profile, does not dominate the recruitment. Purposive sampling by cancer type will be adopted to prevent this. While two of the cancers are female only, stratified sampling will be adopted to ensure all genders are represented in all other cancer groups. If the characteristics of the respondents seem to be strongly biased, we will consider using survey weighting in our analysis, with the weights based on the distribution of patients with advanced cancer in the UK.\(^6\)

Patient and public involvement
This study has been shaped by patient and public involvement (PPI) from inception. PPI has informed the wording of patient-facing documents and how to approach asking patients particularly sensitive questions. PPI will feature prominently across all WSs: plans include patient involvement in interpretation of findings from qualitative interviews; patient feedback on the new questionnaire; and dissemination beyond typical academic routes. The PPI involvement has, and will continue, to take two key formats: (1) having regular meetings with our PPI collaborators (co-authors AB and RB), to discuss the study and provide ongoing support, feedback and advice, and (2) attending PERSPECTIVES, a cancer PPI group, at periodic intervals to discuss the study and provide feedback and advice. Study documents, emerging findings and final results will also be shared at these discussions, with PP representatives invited to provide advice and feedback.

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<th>Table 1</th>
<th>Patient inclusion and exclusion criteria for the TARGET study</th>
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| **Patient inclusion criteria** | 1. Aged 18 years or above  
2. Advanced/metastatic disease  
3. Currently receiving biological and precision therapy for at least 1 month  
4. Completed/discontinued biological and precision therapy within the previous 12 months  
5. Estimated life expectancy >6 weeks* (clinician’s judgement)  
6. Willing and able to give consent |
| **Patient exclusion criteria** | 1. At risk of psychological distress (clinician’s judgement)  
2. Sound understanding of written or spoken English lacking  
3. Capacity to consent lacking (clinician’s judgement)  
4. At the time of recruitment, having chemotherapy or radiotherapy alongside targeted therapy. |

*It can be difficult to ascertain an exact timeline for patients, but clinicians will base their decisions on a variety of factors, including (1) whether there is no active treatment; and (2) treatment not working.

DISCUSSION
This study will provide important insight into the experiences and needs of people with cancer taking biological and precision therapies and deliver a new questionnaire to assess their unmet supportive care needs. It should not be assumed that the needs of patients with cancer taking biological and precision therapies will be the same as people receiving more traditional treatments, such as traditional cytotoxic chemotherapy. It is already well established that biological and precision therapies have different and wide-ranging adverse effects compared with traditional cytotoxic chemotherapy, and as they are taken for long durations, these effects are chronic in nature. Previous unmet needs studies include heterogeneous
cancer patients, some of whom may have been using a targeted agent. Moreover, recent studies assessing the unmet needs of people with advanced cancer did not acknowledge biological and precision therapies. It is important, therefore, to establish the supportive care needs of this patient group, whether their needs are currently being met within current healthcare guidelines and, if not, what could be done to better support people using biological and precision therapies in the future.

Our findings will determine the need for potential additional resources and/or service developments to support the growing population of patients with cancer who receive biological and precision therapies. Population ageing means that the number of people diagnosed with cancer will continue to increase substantially in the coming years. Improving survival means more people will be living with cancer as a long-term condition. Improving patient outcomes through personalised medicine has been identified as a key strategic objective for the UK NHS, and the number of biological and precision therapies for cancer is continually increasing. It is essential that the strategies used—and services provided—to support patients/survivors with cancer, and the associated underpinning research, acknowledge the therapeutic advances of recent years and address the new challenges associated with these. After conducting this exploratory, early-stage work, our intention is to focus on further developing and validating the questionnaire in different populations (e.g., UK residents who do not speak English or other healthcare systems outside of the UK). Only when it is known how to best support patients with, through and (if relevant) after their treatment can the true potential of biological and precision therapies be realised and patient benefits maximised.

ETHICS AND DISSEMINATION

A favourable ethical opinion has been granted from the Tyne and Wear South Research Ethics Committee (REC ref: 21/NE/0028). Standard ethical procedures will be followed including informing participants that participation is entirely voluntary, that they may withdraw at any point without giving a reason and that their participation and data they provide (interview transcripts or questionnaire responses) are confidential and will be anonymised. Informed consent will be sought prior to participation. All patients who take part in an interview will be offered a £20 high-street shopping voucher. This amount is deemed acceptable to thank participants for their time, without coercing them to take part. All identifiable information will be stored securely using REDCap software, which is compliant with HSCN, the secure network communications system used by the NHS, and which will only be accessible by authorised study team members.

Findings will be disseminated via several routes to reach numerous stakeholder audiences including the study website (https://www.ncl.ac.uk/cancer/our-research/toxicity-and-survivorship/target/), social media accounts, presentations at conferences and publications in peer-reviewed journals. All research participants will be offered a summary of the research findings. Advice and suggestions will be sought from our funder, and patient and public involvement, for further dissemination among patient groups.

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Acknowledgements On behalf of the TARGET Project Team, we would like to thank all of our collaborators for their continued support of this study.

Contributors LS, AT, AG and JL developed the idea for the study and secured the funding. LC, AT and LS developed the detailed protocol. LS and AT are joint chief investigators. LC and LS managed the ethical and research approvals. LC is the study coordinator and will conduct the fieldwork and data analysis, with support from the wider research team. MB will be conducting fieldwork and supporting the analysis alongside LC. LS, AT, JL and AG will provide specialised advice throughout the study. MW provided input into the development of the research idea, the study documents and discussing methods of recruitment and will facilitate recruitment. AB and RB are named PPI collaborators and have contributed to the study design, study documents and discussions on study processes. JR is providing significant recruitment support. LC drafted the manuscript. All authors reviewed, edited and approved the final manuscript. MW is supported by NIHR Imperial Biomedical Research Centre (BRC).

Funding This work is funded by a project grant from Macmillan Cancer Support, award number: F0-7165351.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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