BMJ Open

Dynamic treatment regimes (DTRs) to study treatment sequencing in oncology: a scoping review protocol

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To cite: Esteves S, Alves JM, Rodrigues PP, *et al*. Dynamic treatment regimes (DTRs) to study treatment sequencing in oncology: a scoping review protocol. *BMJ Open* 2023;**13**:e067192. doi:10.1136/bmjopen-2022-067192

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-067192).

Received 05 August 2022
Accepted 23 April 2023

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ABSTRACT

Introduction The rapid evolution of the therapeutic landscape in oncology poses challenges to optimal treatment sequencing. Evidence for clinical decision-making is often limited to studies focused on treatment evaluation at a single decision point, with limited capability of identifying delayed effects of prior treatment decisions on the efficacy and feasibility of future treatments. There is a growing interest in dynamic treatment regimes (DTRs) evaluation as it provides guidance on treatment individualisation based on evolving treatment and patient characteristics. In this scoping review we aim to systematically map how and to what extent DTRs have been evaluated in clinical studies to generate evidence for clinical decision-making in oncology.

Methods and analysis We will do a systematic literature search in MEDLINE (PubMed), Web of Science, Scopus and WHO international clinical trials registry platform to identify clinical studies (including protocols of ongoing studies), with either experimental or observational design, that aim to answer a clinical question and explore treatment sequencing issues in oncology using the concept of DTR. Data extraction will comprise information concerning cancer disease, clinical setting, treatments, tailoring variables, decision rules, decision points and outcomes, type of data, study design and statistical methods used for DTR evaluation. The review will be conducted according to Joanna Briggs Institute Reviewer's manual for scoping reviews. No patients will be involved.

Ethics and dissemination Ethics committee approval is not required as this scoping review will undertake secondary analysis of published literature. Results will be disseminated through a peer-reviewed scientific journal and presented in relevant conferences. This scoping review will provide a better understanding of the methods used to generate evidence on treatment sequencing in oncology and will contribute to the identification of knowledge and methodological gaps that should be addressed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will be focused in understanding the methods that are being used to generate evidence to answer clinical questions concerning treatment sequencing in the medical field of oncology and not just in methodological research.
⇒ Our scoping review will conform to the rigorous methodology manual by the Joanna Briggs Institute.
⇒ The literature search will be limited to published articles found in MEDLINE (PubMed), Web of Science and Scopus with a snowballing approach and a search in WHO international clinical trials registry platform to identify ongoing registered clinical trials.

INTRODUCTION

Over the last decade, the landscape of oncology therapeutics has been rapidly evolving, with several new anticancer systemic treatments becoming available. Despite the significant impact of some of these treatments on patients' survival, most oncological diseases remain incurable and chronic, and are characterised by a recurrence pattern that requires a sequence of treatments for long-term disease control. This enrichment of treatment options, with different side effects, cross-resistance patterns and costs present challenges to treatment sequencing decisions, which is paramount to improve the outcomes of the patients and allocate healthcare resources in more efficient ways. One way to study optimal treatment sequencing is through dynamic treatment regimes (DTRs), which have recently become of greatest interest in several medical fields including oncology.[1] Other designations used for DTRs are adaptive treatment strategies, adaptive interventions, multistage treatment strategies, treatment policies and individualised treatment rules. A DTR is a set of sequential decision rules, each corresponding to a key decision point in the progression of a chronic disease, where a decision must be made concerning the next treatment action. Each decision rule takes as input information on the individual patient, disease characteristics and prior treatment (or other time-varying factors that change with the evolution of the disease) and returns the treatment decision that should be made from among the available, feasible options.[2] DTRs

are treatment decision rules that are tailored to the individual patient characteristics and therefore fall within the scope of precision medicine. DTRs can be constructed using data from observational sources such as cohort studies, electronic health records and clinical registries, or experimental studies such as sequential multiple assignment randomised trials (SMART).[2 3] One objective of DTRs research is to construct evidence based on personalised stage-specific treatment decision rules that, when applied to the patient population, will optimise the average expected long-term outcomes of the population of interest.[2] This addresses not only the question 'what treatment when?' but also 'what are the best intermediate outcomes to direct treatment?' and 'how best to individualize treatment decisions based on biological, diagnostic, and other patient information?'.[3] This requires the use of specific methods that handle time-dependent confounding bias and allow modelling of discrete-time or continuous-time interventions and the progression of patient covariates of interest.

We searched PROSPERO, MEDLINE (PubMed), the Cochrane Database of Systematic Reviews and *JBI Evidence Synthesis* for relevant systematic reviews on this topic. We identified a scoping review of studies using observational data to optimise DTRs,[4] a systematic review intended to assess the quality of reporting of SMART,[5] and one protocol of an ongoing systematic review aiming to evaluate the appropriate use and reporting of marginal structural models in the medical literature.[6] This ongoing systematic review is strictly focused on a specific methodology that can be used in the study of DTRs. No reviews, either completed or in-progress, were identified on the topic of evidence generation on treatment sequencing through DTRs evaluation in the oncology medical field.

The scoping review from Mahar *et al*, focused on DTRs optimisation based on observational data.[4] It included 63 studies, 18 had a clear primary focus on informing clinical practice and the remaining 45 used observational data only to illustrate the application of statistical methodology.[4] Overall, this scoping review revealed that the estimation of optimal DTRs from observational data is a recent development (60 out of 63 studies were published after 2005 and 25 after 2017) mainly focused in the areas of HIV/AIDS (n=27), cancer (n=8) and diabetes (n=6).[4] Clinically focused studies were more likely than methodological studies to evaluate time-to-event outcomes (72% vs 51%) and to apply statistical models that used inverse probability weighting (50% vs 38%) or parametric G-formula (44% vs 18%).[4] Although this review provided a general overview of how observational data have been used to estimate optimal DTRs, it should be noted that it did not aim to perform a detailed analysis of the type of clinical questions that have been or need to be addressed in oncology. In addition, it did not address the estimation of optimal DTRs from experimental studies.

The systematic review of SMART studies from Bigirumurame *et al*, aimed to assess the quality of reporting of this type of experimental studies focusing on the basic trial characteristics (research area, sample size calculation information), considerations concerning trial objectives (stage-specific aims, embedded adaptive intervention comparison) and analysis considerations (analysis methods and statistical software).[5] While this review analysed to what extent the most important design features of an SMART are adequately reported in the literature, it did not assess design features specifically used in oncology studies.

As treatment sequencing is increasingly becoming a critical issue in research and clinical practice in chronic diseases including cancer, we consider that a scoping review concerning the evaluation of DTRs in oncology research can provide a better understanding of the effective use of this concept to study treatment sequencing and contribute to the identification of knowledge and methodological gaps that should be addressed.

METHODS AND ANALYSIS

The use of DTRs to generate evidence on treatment sequencing has a conceptual appeal that stems from its clear resemblance to clinical practice in the way that it tailors treatment decisions to different individuals and within individuals across time. We believe that this approach brought a new perspective to the study of treatment sequencing and has high applicability to clinical practice, even though it is still underused. We aim to perform a comprehensive characterisation comprising the study design features, the type of source data, the analytical approaches used, the type of decision problems, the clinical context and the aim of the study (as assessed by the Patient-Intervention-Comparator-Outcome framework) that are being used to generate evidence concerning treatment sequencing decision problems in oncology. As such, we hope that this scoping review will provide a better understanding of the methods that are actually being used to generate evidence (and not the theoretical models or purely methodological research) and will contribute to the identification of knowledge and methodological gaps that should be addressed. We will follow a rigorous methodological approach to systematically find, select and synthesise all available evidence. One limitation of our study is that the literature search will be limited to published articles and ongoing clinical trials registered in WHO registry platform.

The proposed scoping review will be conducted in accordance with methodology manual for scoping reviews published by the Joanna Briggs Institute,[7] and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews.[8] The study was started in November 2022 and the planned end date is August 2023.

Patient and public involvement

No patients will be involved.

Stage 1: identification of research questions

Our overall aim is to understand how and to what extent the concept of DTR is being used in oncology research

Table 1 PCC framework for our scoping review

PCC element	Definition
Population	Human subjects with any type of cancer disease.
Concept	Use of dynamic treatment regimes to study treatment sequencing issues.
Context	Clinical research studies of any design that aim to answer a clinical question regarding the systemic treatment of a cancer disease.

to address clinical questions concerning treatment sequencing. This translates into the following specific research questions:

1. What types of data are used for optimal DTR evaluation in oncology studies (experimental studies vs observational studies vs registry data)?
2. Has this concept been mostly used in any particular disease or treatment setting?
3. Is there a pattern in the way key elements of DTRs evaluation are defined in oncology (type of tailoring variables, decision stages, type of treatment, decision rules)?
4. What are the endpoints considered?
5. What statistical methods are being used to estimate optimal DTRs?
6. What is the (experimental) study design most frequently used and what are the primary questions addressed?

We ultimately aim to use this information to discuss knowledge gaps that limit its application in oncology research.

Stage 2: identifying relevant studies

This review will use the PCC (Population, Concept, Context) framework suggested in the Joanna Briggs Institute manual.[7] The search strategy and the eligibility criteria will be based on this PCC framework described on table 1.

Search strategy

The search strategy will be based on the PCC framework and will aim to locate published studies, reviews and protocols of ongoing studies. We will search the databases MEDLINE (PubMed), Web of Science and Scopus. In addition, the WHO international clinical trials registry platform (https://trialsearch.who.int/) will be searched to identify ongoing studies.

An initial exploratory search on MEDLINE (PubMed) was undertaken to identify relevant terms and articles on the topic. The text words contained in the titles and abstracts of relevant papers, and the index terms used to describe the papers, were used to develop a pilot search strategy (online supplemental appendix A). The search strategy, including all identified keywords and index terms concerning the major themes 'cancer' and 'DTR', will be adapted for each included database and/or information source. The reference lists from the included papers and from the retrieved systematic reviews on this topic will be screened for additional papers in a snowball searching approach. We will focus on articles published after 2000 in English, Portuguese, Spanish and French. Our focus on papers posterior to 2000 is justified because we are aiming to characterise the current application of DTR concept in oncology research. In addition, it should be noticed that the seminal papers from Robins *et al* proposing the causal inference models that have been applied in the study of optimal DTRs were published in the late 1990s.

Stage 3: selection of eligible studies

Following the search process, all identified records will be collated and uploaded into Zotero reference manager (https://www.zotero.org/) in order to remove all duplicates. This list will be imported into Rayyan,[9] a free web tool for conducting collaborative systematic reviews. A two-stage screening will be performed. In the first stage we will screen the titles and abstracts. An initial pilot test will be conducted to ensure clarity and consistency in the application of the eligibility criteria during title and abstract screening. Following the pilot test, titles and abstracts will then be screened by two independent reviewers for assessment against the eligibility criteria. Potentially relevant papers will be retrieved in full and imported again into Rayyan.[9] The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer. The results of the search will be reported in full in the final scoping review and presented in a PRISMA flow diagram.[10]

Eligibility criteria

This review will consider clinical studies that include patients with any cancer disease. This review will include studies that explore systemic treatment sequencing issues using the concept of DTR. This concept requires the evaluation and/or comparison of multistage interventions/treatments and the identification/study of a decision rule for each treatment stage that is based on an intermediate outcome or other tailoring variable. Studies that only describe outcomes of sequences of interventions with no attempt to explore tailoring variables or decision rules will be excluded. We will consider clinical research studies that aim to answer a clinical question regarding the systemic treatment of a cancer disease. Methodological studies that use simulated data or provide only a theoretical discussion or a review on methods for DTRs evaluation and non-clinical studies (eg, that analyse in vitro data or data from non-human subjects) will be excluded.

This scoping review will include clinical research studies with any experimental, quasi-experimental or observational design. Primary research studies, secondary analyses of trial data and study protocols will

all be considered for inclusion provided they involve the study of DTRs in the medical field of oncology. Systematic reviews focusing on this topic will be used to screen for additional studies from their reference lists. Book chapters, conference abstracts/posters, clinical guidelines, theses, manuals/technical reports and papers that provide a commentary, review, opinion or description only will be excluded.

Stage 4: charting the data

Data will be extracted from papers included in the scoping review by two independent reviewers using a data extraction table developed by the reviewers. If necessary, this extraction tool can be modified and revised during the process of data extraction. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

The data extracted will include the following key elements:

1. Complete reference: title; authors; year of publication; publication source.
2. Sources of funding.
3. Country of origin.
4. Data type (eg, observational study, experimental study, registry).
5. Details on study design (eg, retrospective data collection).
6. Primary research question addressed by the study.
7. Cancer disease.
8. Treatment setting/context (eg, first line followed by maintenance treatment).
9. Type of intermediate (if applicable) and long-term outcomes considered.
10. Number and short description of decision points/treatment stages.
11. Treatment options evaluated.
12. Tailoring variables.
13. Short description of decision rules.
14. Number of patients.
15. Statistical model used for DTRs evaluation including relevant technical specifications.
16. Methods used to deal with missing data.
17. Methods used for covariate and tailoring variables selection (eg, domain knowledge, cross-validation).
18. Methods used for sensitivity analysis (if any).
19. Libraries and software used in the analyses and source code included (yes/no).

Stage 5: collating, summarising and reporting of the results

The purpose of this scoping review is to collect and summarise the evidence on the use of the DTR concept in oncology research to address clinical questions concerning treatment sequencing. As such we intend to present an overview of the published research rather than evaluate the quality of the studies.

Data will be extracted at the study-level and descriptive statistics will be used to synthetise the results. Results will be primarily presented in tables accompanied by a narrative summary, with graphical outputs to be considered at the time of analysis. Depending on the number of studies identified, the presentation of the results may be divided by subgroups according to the type of data, study design, cancer disease or methodological topics.

ETHICS AND DISSEMINATION

We expect that the results of this scoping review will be informative for different stakeholders including not only the professionals directly involved in this research field such as clinical investigators, statisticians and data scientists, but also the clinicians and public health agencies, as evidence generation concerning treatment sequencing has an extensive application in clinical decision-making and policy definition. Ethics committee approval is not required as this scoping review will undertake secondary analysis of published literature. Results will be disseminated through a peer-reviewed scientific journal and presented in relevant conferences.

Contributors Design of the protocol—SE, JMA, PPR and MGdS. Draft of the manuscript—SE. Review and final approval of the manuscript—SE, JMA, PPR and MGdS.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix A: Search strategy for a scoping review protocol on the use of Dynamic Treatment Regimes (DTRs) to study treatment sequencing in oncology

STEPS:

1. Search strategy developed on the PubMed/MEDLINE database after iterative refinement

Search	Search terms /Description
#1	"causal inference"[All Fields] OR "time-varying confound*"[All Fields] OR "adaptive intervention*"[All Fields] OR "adaptive treatment*"[All Fields] OR "adaptive therap*"[All Fields] OR "dynamic intervention*"[All Fields] OR "dynamic treatment*"[All Fields] OR "treatment sequenc*"[All Fields] OR "treatment polic*"[All Fields] OR "multistage treatment*"[All Fields] OR "multi-stage treatment*"[All Fields] OR "combined-modality treatment*"[All Fields]”
#2	("random*"[Title/Abstract] AND ("maintenance"[Title/Abstract] OR "intensification"[Title/Abstract] OR "consolidation"[Title/Abstract])) OR ("sequential"[All Fields] AND "multiple"[All Fields] AND "random*"[All Fields] AND "trial"[All Fields]) OR "sequential multiple assignment randomized trial"[All Fields] OR "smart design"[All Fields] OR "second random*"[All Fields] OR "multiple randomi*"[All Fields] OR "multi-stage trial"[All Fields] OR "two-stage trial"[All Fields] OR "sequential multiple assignment randomised trial"[All Fields] OR "two-stage random*"[All Fields] OR "subsequent* random*"[All Fields] OR "optimal timing"[Title/Abstract] AND "therapy"[Title/Abstract]
#3	neoplasms/therapy[MeSH Terms] OR "cancer*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "oncolog*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR hematopoietic stem cell transplantation[MeSH Terms] OR "bone marrow transplant*"[Title/Abstract]
#4	(#1 OR #2) AND #3

2. Adapt the search strategy to Embase/Ovid and Scopus databases
3. Search the WHO international clinical trials registry platform (https://trialsearch.who.int/) for ongoing clinical trials in oncology involving the study of treatment sequences.