



STUDY PROTOCOL

REVISÉD **Mapping the use of Group-Based Trajectory Modelling in medication adherence research: A scoping review protocol [version 2; peer review: 3 approved]**

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Abstract

The use of group-based trajectory modelling (GBTM) within the medication adherence literature is rapidly growing. Researchers are adopting enhanced methods to analyse and visualise dynamic behaviours, such as medication adherence, within 'real-world' populations. Application of GBTM based on longitudinal adherence behaviour allows for the identification of adherence trajectories or groups. A group is conceptually thought of a collection of individuals who follow a similar pattern of adherence behaviour over a period of time. A common obstacle faced by researchers when implementing GBTM is deciding on the number of trajectory groups that may exist within a population. Decision-making can introduce subjectivity, as there is no 'gold standard' for model selection criteria. This study aims to examine the extent and nature of existing evidence on the application of GBTM for medication adherence assessment, providing an overview of the different GBTM techniques used in the literature. The methodological framework will consist of five stages: i) identify the research question(s); ii) identify relevant studies; iii) select studies; iv) chart the data and finally, v) collate, summarise and report the results. Original peer-reviewed articles, published in English, describing observational and interventional studies including both concepts and/or sub-concepts of GBTM and medication adherence or any other similar terms, will be included. The following databases will be queried: PubMed/MEDLINE; Embase (Ovid); SCOPUS; ISI Web of Science and PsychInfo. This scoping review will utilise the PRISMA extension for Scoping Reviews (PRISMA-ScR) tool to report results. This scoping review will collect and schematise different techniques in the application of GBTM for medication adherence assessment

Open Peer Review

Reviewer Status ✓ ✓ ✓

	Invited Reviewers		
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version 2			
(revision)	✓		✓
05 Aug 2020	report		report
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version 1	✓	✓	✓
19 May 2020	report	report	report

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Any reports and responses or comments on the article can be found at the end of the article.

available in the literature to date, identifying research and knowledge gaps in this area. This review can represent an important tool for future research, providing methodological support to researchers carrying out a group-based trajectory analysis to assess medication adherence in a real-world context.

Keywords

Medication Adherence, Patient Compliance, group-based trajectory modelling, scoping review, pharmacy refill claims, dispensing, longitudinal, trajectory analysis

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REVISED Amendments from Version 1

Version 2 of this scoping review protocol includes suggestions from reviewers. The abstract has been amended to reflect the updated inclusion criteria. A sentence on the most commonly used adherence measures within pharmacoepidemiological databases was included. Guided by feedback from reviewers, the inclusion criteria has been amended to include relevant randomised controlled trials at the abstract stage. As stated in the revised protocol, study abstracts will need to indicate that longitudinal analyses have been performed in order to be included. Due to the large volume of results retrieved in initial database searches, the screening process has been modified to ensure efficient completion of the scoping review. The data extraction template has been modified to include additional items as suggested by the reviewers.

Any further responses from the reviewers can be found at the end of the article

Introduction

Medication adherence is generally described as the process by which people take their medication as prescribed or as agreed with their prescriber. A taxonomy has been developed to describe the three distinct, yet, inter-related processes involved in medication adherence; initiation, implementation and discontinuation¹. Initiation adherence refers to the first prescription for the medication being dispensed in the pharmacy. The implementation phase refers to the execution of the recommended dosing regimen; skipping doses, delaying refills or taking drug holidays are examples of implementation non-adherence. Discontinuation occurs when the patient stops taking the medication, thus beginning a period of non-persistence. Persistence is another term that is commonly used and refers to the duration the patient takes the medication for, encompassing the initiation and implementation phases¹. Initiation, discontinuation and persistence are usually modelled as time-to-event phenomena, whereas implementation adherence can be reported in a variety of ways, usually involving summary statistical estimates². Summary adherence estimates include measures such as the proportion of days covered (PDC) and medication possession ratio (MPR), which are commonly used to describe adherence using administrative claims data².

However, adherence is a dynamic behaviour, potentially varying over time due to a number of factors. It has been suggested that longitudinal methods should be used to analyse implementation adherence, as aggregating behaviours over time into a single summary estimate of adherence which is then dichotomized can result in a loss of information about the detailed patterns of adherence^{1,3}. This is of particular concern for the estimation of adherence to medications used to treat long-term, chronic conditions. Using summary measures can often lead to difficulty in estimation of the time point or phase at which non-adherence is likely to occur in a population. Indeed, two individuals may have the same average adherence value over a period of time (i.e. 50%) but one may skip doses regularly, whereas the other may have had high initial adherence followed by a long gap in dispensing³. Over the past number of years, group-based trajectory

modelling (GBTM) has become more frequently applied in adherence research, to enhance understanding of adherence behaviours³. This is due to the availability of freely available, downloadable software programmes that can be used within existing statistical packages to implement GBTM⁴. Indeed, GBTM has been recently applied to older Irish populations to identify trajectories based on adherence to anti-hypertensive medications^{5,6} and across multimorbidity^{7,8}. Identification of groups vulnerable to poor adherence and the time-point at which this can occur in the treatment process may help to inform targeting of medication management interventions.

GBTM is a type of finite mixture modelling which uses trajectory groups to estimate an unknown distribution of trajectories that exist within a population⁹. The groups identified by the models should not be thought of as literal entities, but rather as discrete groups that may exist within a population⁹. Considering the application of GBTM within adherence research, a group is conceptually thought of as a collection of individuals who follow approximately the same pattern of adherence behaviour, equivalent to a contour line on a contour map⁹. GBTM is operationalised by repeatedly measuring adherence at frequent time intervals (i.e. monthly) and grouping individuals with similar longitudinal adherence patterns¹⁰. GBTM may aid the precise identification of the timing of transition from one adherence phase to another, namely movement from the implementation phase into the discontinuation phase. The model assumes that within-person correlation is explained completely by the adherence trajectory curve estimated for each person's group¹⁰. Model parameters are estimated using maximum likelihood⁴, meaning unbiased estimates can be produced in the presence of missing data, provided such data are missing at random⁹.

A common obstacle faced by researchers when implementing GBTM is deciding on the number of trajectory groups that may exist within a population. Prior to conducting any statistical analysis, the maximum number of groups likely to exist based on the size of the population and existing evidence is estimated. However, adherence is often reported as a dichotomous variable in the literature, resulting in participants being classified into two adherence groups; adherent and non-adherent. The threshold most commonly used to determine this classification has been arbitrarily set at 80%^{3,11}, originating from anti-hypertensive medication studies^{12,13}, with little validation across other conditions. Therefore, *a priori* theories on the number, shape and size of adherence trajectory groups are often absent⁹.

Determining the number of optimum number of adherence groups that hypothetically exist within a population is based on statistical fit indices, most commonly the Bayesian Information Criteria (BIC)¹⁴, Akaike Information Criteria (AIC)¹⁵, Lo-Mendall-Rubin likelihood ratio test (LMR-LRT)¹⁶ and entropy⁹. BIC and AIC aim to identify the most parsimonious model by balancing model complexity versus goodness to fit to the study data⁹. Lower index values indicate improved model fit. The LMR-LRT utilises a likelihood-ratio-based approach, helping to determine the optimum model between 'k-1' and k class models; a p value >0.05 is used to reject a new model class containing

an additional group (k)^{9,17}. Entropy is used to measure how accurately the model classifies participants into different trajectories or groups. The average posterior probabilities of group membership are calculated with values closer to 1 indicating greater precision. Previous adherence GBTM studies have used thresholds of probability ≥ 0.70 to indicate presence of sufficient entropy in a model^{7,17}, whereas others did not use explicit cut-offs^{5,6,10}.

Rationale

To date, and to the best of our knowledge, there is no existing peer-reviewed or published synthesis of the use of GBTM in medication adherence research. As the popularity of GBTM is growing in the adherence literature, it is necessary to map the evidence within this area, to help summarise existing evidence and guide future research. A scoping review methodology is used for such a mapping exercise as it is suited to broad research questions and is useful in fields such as adherence measurement, where there is a lot of measurement heterogeneity¹⁸. Scoping reviews not only highlight the extent of research available on a topic, but also allow for a description of the conduct of such research¹⁸. A synthesis of the literature of the use of GBTM in medication adherence measurement will help to identify research deficits and knowledge gaps in this area, informing future research¹⁸⁻²⁰.

Objective and aims

The objective of this scoping review is to describe the nature, number, scope and methodology of published research articles using group-based trajectory modelling to measure medication adherence and to identify what further research is required.

Specifically, we will aim to:

- Systematically explore the extent of relevant empirical literature on the use of group-based trajectory analysis applied to medication adherence in longitudinal studies.
- Map and categorise publications obtained according to the following taxonomy: purpose of study (identify adherence behaviours, groups for intervention targeting), model selection criteria used to determine adherence groups, and outcomes typology (validation against clinical/other health outcomes or absent).
- Provide an overview of the different GBTM techniques used for medication adherence measurement in the literature and guidance for future adherence research.

Methods

The methodological framework for conducting this scoping review was informed by published guidance¹⁸⁻²⁰. This process consists of five different stages:¹⁹ (1) identify the research question(s); (2) identify relevant studies; (3) select studies; (4) chart the data and (5) collate, summarise and report the results. There is an optional sixth stage, 'consultation with relevant stakeholders' that may be prioritised in social science research²⁰. However, the relevance of this stage in the current scoping review is not apparent, and as such we will not be formally engaging with external stakeholders prior to completion of the scoping review.

In order to provide a descriptive account of the status of GBTM in adherence research and identify knowledge gaps, a scoping review of the literature is most appropriate. Findings from the review may help to promote standardisation of GBTM methodology in future adherence studies. As in the case of systematic reviews, scoping reviews also use a systematic approach to research, screening and reporting.

Identifying the research question

There has been an increasing use of GBTM as a tool for longitudinal adherence measurement and visualisation; however, there appears to be a lack of standardisation in the methodological approach similar to the existing heterogeneity in medication adherence measurement^{21,22}. The lack of standardisation can introduce varying degrees of subjectivity into the decision-making process required with application of GBTM, limiting comparison across studies. While some degree of subjectivity may be necessary²³, it would be advantageous to summarise the various approaches used to help inform future research. The following research questions were identified for the review based on the aims of the review:

1. What is main purpose of application of GBTM in medication adherence research?
2. What is the range of statistical techniques employed to apply GBTM for the measurement of medication adherence in the literature?
3. Which clinical or other outcomes been used to validate the use of GBTM in medication adherence research?
4. Is the use of GBTM for measurement of medication adherence prominent in specific populations or cohorts? Are there differences in methodological approaches consequentially?
5. Are there recommendations for the standardisation of GBTM techniques within adherence research?
6. What are the current knowledge gaps relating to the application of GBTM in medication adherence research that require further research?

Identification of additional research questions may be an iterative process, informed by emerging themes that appear while conducting the scoping review.

Identifying relevant studies

Inclusion criteria. Peer-reviewed publications of empirical research which apply GBTM to the measurement of medication adherence will be considered for inclusion. Furthermore, publications will have to include in their abstract both concepts and/or sub-concepts of group-based trajectory modelling or any other similar term (e.g., group-based analysis, trajectory model) and medication adherence.

Original articles, published in English, describing observational studies will be included. No restrictions will be placed on study design (case-control, cohort, prospective, retrospective etc), although it is unlikely cross-sectional studies will be suitable,

given the need for longitudinal data to perform GBTM. Randomised controlled trials will be included if it is specified in the study abstract that longitudinal analysis was performed as part of the study.

In the first instance, no limitations will be applied in the year of publication, therefore, all studies in the literature to date will be identified. However, if excessive search results are identified after de-duplication (>4000), search results will be narrowed to articles published after January 2005, as it is after this time that GBTM mainly emerged in the medication adherence field.

Exclusion criteria. Only articles available in English will be included. Furthermore, grey literature including guidelines, booklets, reports, and clinical guidelines will not be included. Unpublished academic documents such as theses and dissertations will be not included in the scoping review. In addition, conference abstracts will not be considered as the purpose of this scoping review is to extract data relating to the methodological approach used in GBTM studies, of which abstracts provide limited detail. Similarly, study protocols will be excluded as hypothetical analytic approaches may differ from actual methodological approaches applied. However, we will attempt to contact authors of relevant protocols and abstracts to ascertain the availability of full research reports, if not identified by the existing search. Systematic and literature reviews will not be included in the review, but instead, will be used to identify potentially relevant observational studies.

Information sources and search strategy. For the present scoping review, the identification of relevant studies will be achieved by searching electronic databases of the published literature, which will include the following: Medical Literature Analysis and Retrieval System Online (PubMed/MEDLINE); Embase (Ovid); SCOPUS; ISI Web of Science and PsychInfo. A comprehensive search strategy has been developed with the assistance of a medical librarian, to identify relevant studies. Search terms were determined by team members and further developed after consultation with the medical librarian. Search strings combined keywords, phrases and Medical Subject Headings (or equivalent) across two concepts using the AND Boolean operator: (1) medication adherence; (2) group-based trajectory modelling. Terms for medication adherence were informed by a previous systematic review involving some of the authors²², and expanded upon. Search terms relating to 'medication adherence' include patient compliance, treatment adherence, medication (non-) compliance, medication persistence as well as the phases of medication adherence as per the ABC taxonomy (initiation, implementation, discontinuation)¹. For 'group-based trajectory modelling', related terms include 'gbtm', 'trajectory analysis', 'longitudinal trajectory' and 'adherence pattern'. Within each concept, relevant terms were combined using the 'OR' Boolean operator. The search strategy was developed for use in PubMed/Medline and will be further adapted for use across the four other electronic databases. The full search strategy will be included in the final manuscript. Electronic databases

will be searched from inception, with no limitations or filters placed on records obtained, until acceptance for publication.

Further, a citation search of included full-texts will be undertaken in Google Scholar to identify relevant published studies that were not retrieved through database searching.

Selecting relevant studies

The search results will be downloaded to an electronic referencing system and duplicates removed. As stated previously, should an excessive number of independent records be retrieved, records will be limited to those published during or after 2005. One author (CW) will independently screen the title and abstracts of all retrieved articles for studies that use GBTM to measure medication adherence. A second reviewer (SM) will independently screen a 50% random sample of abstracts. Abstracts that are deemed unsuitable for progression to full-text review will be allocated to folders citing the reason for exclusion. Once each reviewer has selected relevant records for full-text review independently, results will be compared between reviewers and discussions held until consensus is reached. The second reviewer will review the abstracts, excluded from their random sample, that were selected for full text review by the main reviewer. If a conflict remains following discussions, a third reviewer (CC or EM) will be consulted until consensus is reached. Two reviewers (SM and CW) will review each full text independently, citing reasons for exclusion if not deemed suitable for inclusion in the scoping review. Discussions will be held until consensus is reached, adhering to the inclusion and exclusion criteria specified *a priori*. Similar to the abstract screening process, a third reviewer will be consulted (CC or EM) to resolve any conflict. Reasons for exclusion of texts after full-text review will be documented and reported in the PRISMA study flow diagram.

Charting the data

A standardised data charting form was created in Excel *a priori*, based on guidance pertaining to data charting in scoping reviews from the Joanna Brigg's Institute Reviewer's Manual²⁴. We have updated the form based on useful suggestions provided by protocol reviewers. Initial categories included general study characteristics such as authors, title, DOI, year of publication and country. Next, information on the study design will be collected including the aims/purpose of the study, whether adherence was modelled as an exposure, covariate or outcome, descriptives of the study population and sample size (e.g. age, gender, and ethnicity) and the medication or disease group studied. Further, information specific to medication adherence measurement will be collected including the data source, duration of adherence measurement (length of observation), the time intervals used, the GBTM method applied (statistical package used), the maximum number of adherence trajectories selected, along with the evidence base used to inform this number, if applicable, and finally, the model selection criteria used to select the optimum number of adherence trajectories. Information on the order used (cubic, quadratic etc) to model groups will be extracted, if available. Lastly, information pertaining

to results and findings from the study will be extracted, including the number of adherence trajectories identified, details relating to validation against clinical outcomes, if applicable, and any adjustment for covariates and limitations of the study. Initially, the data charting form will be piloted using two or three relevant studies identified from database searches. This will be done independently by two reviewers (SM and CW) and discussions will be held between the two reviewers following this to identify additional data that needs to be charted, along with amendments of existing headings if required^{19,20}. Study authors will be contacted if further clarification is required in relation to data extracted.

Collating, summarising and reporting the results

This scoping review will utilise the PRISMA extension for Scoping Reviews (PRISMA-ScR) tool²⁵. A flow diagram will be used to outline the selection of data sources, including descriptive reasons for exclusion at the full-text review stage. Characteristics of the included studies will be described based on the descriptive headings in the data extraction form. Specifically, the evidence will be summarised and reported using the taxonomy described in the aims; purpose of the study, model selection criteria use and outcomes typology (if applicable). Guided by the research questions, additional headings will be used to summarize the studies if findings are not sufficiently communicated using the aforementioned taxonomy. For instance, it may be possible to categorise studies based on their study population (paediatric vs older people) or disease area (cardiovascular, musculoskeletal etc). Formal quality appraisal of included studies will not be undertaken, as the aim of scoping reviews is to provide an overview of the existing evidence base regardless of quality¹⁸. A general interpretation of the evidence will be provided, as well as identification of potential knowledge gaps. The strengths and limitations

of the scoping review will be outlined, as well as potential guidance for future research in the final report. Any deviations from this protocol, including reasons, will also be detailed.

Conclusion

The over-arching purpose of GBTM is to identify discrete groups that have meaningful differences in terms of pre-existing characteristics or subsequent outcomes or treatment response. If the groups or trajectories cannot be distinguished on the basis of such dimensions, identification of different trajectories serves little purpose⁹. This scoping review will collect and schematize different techniques in the application of group-based trajectory modelling for medication adherence assessment available in literature to date. The main expectation of the exploration of the literature will be to summarise evidence and identify research and knowledge gaps in this area to inform future research. Indeed, recent studies have called for greater transparency over the subjective decisions involved in applying GBTM for medication adherence assessment²³. This review may represent an important tool for future research, in order to methodologically support researchers who will be carrying out group-based trajectory analysis to assess medication adherence in real-world contexts.

Data availability

No data are associated with this article.

Acknowledgments

We would like to acknowledge the assistance of Paul Murphy, Information Specialist at the Royal College of Surgeons in Ireland, in creating and translating the search strategy for use across databases.

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Open Peer Review

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 **Ryan P. Hickson** 

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Thank you for your thoughtful responses to my comments. Looking forward to when this review is complete. I do not require any new changes, but would like to state I still find the definition of entropy confusing at the end of the introduction. I have seen papers use the maximum posterior probabilities themselves to evaluate GBTM model fit (the distribution of posterior probabilities for each group are evaluated, so if you have 4 groups, you are evaluating 4 separate averages), and I have seen papers use entropy - which uses posterior probabilities in its calculation - to evaluate GBTM model fit (a single entropy estimate is provided for the full model, so no matter how many groups are in the model, you are only evaluating 1 entropy estimate for model fit). I think equations 12 and 13 and the following paragraphs help illustrate this distinction in this paper¹. I only bring this up as it seems these concepts are not clearly explained/understood in all of the medication adherence GBTM papers I have read.

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Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medication adherence, pharmacoepidemiology, population health science, causal inference, cardiometabolic conditions.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 05 August 2020

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Hannah Durand 

School of Psychology, National University of Ireland, Galway, Ireland

I have no further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medication adherence; quantitative methods; evidence synthesis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 June 2020

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Ryan P. Hickson 

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Paper summary and general comments

This paper is a protocol describing a proposed scoping review of the use of group-based trajectory modelling (GBTM) in the medication adherence literature. The rationale for this review is strong, and once completed, this review should be of great interest to medication adherence researchers, especially those wishing to use a GBTM analysis. Particularly, the identification of relevant studies, search strategy, selecting relevant studies, data charting, and collating are well described. This makes the search strategy reproducible for others and will help readers easily understand the scope of what was reviewed. My only concern is that the rationale for excluding any potential randomized studies that use GBTM to assess medication adherence does not seem justified.

Specific comments

Major

Introduction, paragraph 4: This paragraph is unclear to me. You seem to be talking about 2

different concepts: (1) how many latent groups to use for the GBTM, and (2) whether to use continuous adherence measures (ranging from 0% to 100%) or binary adherence measures (e.g. an 80% cutoff) which would then be modeled as a continuous GBTM (CNORM distribution) or a binary GBTM (LOGIT distribution), respectively. Consider revising.

Introduction, paragraph 5: I believe your use of “entropy” and “posterior probabilities” is confusing and misleading here. Each individual is assigned a posterior probability of belonging to each of the groups in the GBTM. The average maximum posterior probability (averaging the posterior probabilities within each group, but only including posterior probabilities for individuals assigned to the given group) is one method used to assess the model fit¹. Entropy and relative entropy are also measures of model fit that use posterior probabilities in its calculation, but it is not a simple average of posterior probabilities; only relative entropy is bound between 0 and 1²

Exclusion criteria. I doubt you will find many if any randomized trials using GBTM for medication adherence; however, I would recommend against excluding RCTs outright. Patients would not be randomized to adherence groups; GBTMs in this setting may not be “real-world” because it is in a restricted population eligible for an RCT; however, GBTM is still measuring the “real-world” medication-taking behavior for patients assigned to a given intervention.

Charting the data: “duration of adherence measurement”. Does this refer to how long adherence was measured (e.g. 6 months vs. 12 months)? Or to the time-intervals in which adherence was measured (e.g. 30 1-day intervals for 1 month of longitudinal adherence; 6 30-day intervals for 6 months of longitudinal adherence)? Both of these concepts would be important.

Minor

General: consider reviewing paper for minor typos, etc. to improve readability.

Abstract: “This study aims to examine the extent and nature...” It is not clear what this means, consider revising.

Introduction, end of paragraph 1: “... usually involving summary statistical estimates”. This is unclear. Perhaps an example would help clarify.

Introduction, paragraph 3: you state that GBTM has been used for the past 15 years. Are you sure this is accurate? I had thought Franklin *et al.* was the first to use GBTM for medication adherence in 2013³, but the review you cite⁴ shows an earlier paper by Modi *et al.* in 2011 that used GBTM for medication adherence⁵. However, I do not see or know of any GBTM papers for medication adherence that were published before this.

Rationale: “mapping” and “scoping review” may be standard terminology for this type of review, but consider giving a clearer definition of these terms earlier in the paper. Readers of your final paper, specifically researchers who want to use GBTM for medication adherence projects, may not be familiar with these terminologies.

Objective and aims: What do you mean by “nature” and “extent”?

Methods, paragraph 1 and throughout. For stage (1), “identify the research question”, I believe

clarification is in order. May be difficult for reader to understand if this means research questions as it relates to your review, or the research questions of the papers you are reviewing.

Search strategy. I believe the search terms are fairly well-defined, but a table may help to better visualize all the possible combinations and how the Boolean operators are applied. Additionally, for medication adherence search terms, what about the terms “adherence” and “compliance”, etc., without the word medication directly in front of it? Would you potentially be missing some papers who never explicitly said “medication adherence”? What about wildcards? E.g. adheren* to capture adherence and adherent?

Charting the data: What about how medication adherence was modeled as a function of time? All cubic? All quadratic? A mixture of 0-order through quartic?⁶

Charting the data: It is unclear if this is mentioned elsewhere, but what about the purpose of the GBTM. Are the groups meant to be an exposure, with associations with clinical outcomes the purpose? Are the adherence groups the outcome of the study, to understand patterns of adherence in normal practice or as part of an intervention to change adherence? Or are the groups meant to adjust for health-seeking behavior? Other potential purposes....

Conclusion: “The over-arching purpose...” Are these the only reasons to use GBTM for medication adherence studies? What about measuring medication adherence simply to observe what the behavior is? Or as a health-seeking behavior to adjust for the healthy user/sick stopper bias?

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1. Nagin DS: Group-based modeling of development. *Harvard University Press*. 2005.
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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medication adherence, pharmacoepidemiology, population health science, causal inference, cardiometabolic conditions.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 25 Jul 2020

Caroline Walsh, Royal College of Surgeons in Ireland, Beaux Lane House, Lower Mercer's Street, Dublin 2, Ireland

Paper summary and general comments

This paper is a protocol describing a proposed scoping review of the use of group-based trajectory modelling (GBTM) in the medication adherence literature. The rationale for this review is strong, and once completed, this review should be of great interest to medication adherence researchers, especially those wishing to use a GBTM analysis. Particularly, the identification of relevant studies, search strategy, selecting relevant studies, data charting, and collating are well described. This makes the search strategy reproducible for others and will help readers easily understand the scope of what was reviewed. My only concern is that the rationale for excluding any potential randomized studies that use GBTM to assess medication adherence does not seem justified.

Response:

Thank you for your suggestions. We have responded to specific comments below and in the manuscript as indicated.

Specific comments

Major

Introduction, paragraph 4: This paragraph is unclear to me. You seem to be talking about 2 different concepts: (1) how many latent groups to use for the GBTM, and (2) whether to use continuous adherence measures (ranging from 0% to 100%) or binary adherence measures (e.g. an 80% cutoff) which would then be modeled as a continuous GBTM (CNORM distribution) or a binary GBTM (LOGIT distribution), respectively. Consider revising.

Response:

Thank you. The review is about the number of trajectories to use for the GBTM. We are not referring to the nature of the indicator adherence variable (continuous vs dichotomous) to be used in the GBTM and we do not mention that here. To clarify we have added 'in the literature' to the following sentence: 'However, adherence is often reported as a dichotomous variable in the literature'

In adherence studies we often get 2 exposure/outcome groups based on dichotomisation of

the adherence variable; adherent and non-adherent. As such, it can be difficult to specify a priori the maximum number of adherence groups that might exist within a certain population, unless GBTM has been previously carried out in a similar population or medication group.

Introduction, paragraph 5: I believe your use of “entropy” and “posterior probabilities” is confusing and misleading here. Each individual is assigned a posterior probability of belonging to each of the groups in the GBTM. The average maximum posterior probability (averaging the posterior probabilities within each group, but only including posterior probabilities for individuals assigned to the given group) is one method used to assess the model fit¹. Entropy and relative entropy are also measures of model fit that use posterior probabilities in its calculation, but it is not a simple average of posterior probabilities; only relative entropy is bound between 0 and 12

Response:

Thank you. In a 2010 article from Nagin and Odgers(1), the following is stated in relation to entropy; ‘ Entropy is also used in model selection, as it indexes classification accuracy by averaging the posterior probabilities after individuals have been assigned to their most likely class, with values closer to 1 indexing greater precision (range 0 to 1).’ Having a minimum proportion (usually 5%) within each group is also used as a measured of model fit. We have added the following to the manuscript: ‘Estimation of the average posterior probabilities of group membership is included in the entropy calculation.’

Exclusion criteria. I doubt you will find many if any randomized trials using GBTM for medication adherence; however, I would recommend against excluding RCTs outright. Patients would not be randomized to adherence groups; GBTMs in this setting may not be “real-world” because it is in a restricted population eligible for an RCT; however, GBTM is still measuring the “real-world” medication-taking behavior for patients assigned to a given intervention.

Response:

We have modified the criteria as outlined in the reviewer response previously.

Charting the data: “duration of adherence measurement”. Does this refer to how long adherence was measured (e.g. 6 months vs. 12 months)? Or to the time-intervals in which adherence was measured (e.g. 30 1-day intervals for 1 month of longitudinal adherence; 6 30-day intervals for 6 months of longitudinal adherence)? Both of these concepts would be important.

Response:

Thank you for highlighting this omission and we agree. We think both length and time intervals are important data to extract from studies. We have amended the ‘charting the data’ section to state as follows: ‘Further, information specific to medication adherence measurementduration of adherence measurement (length of observation), the time intervals used.....’

Minor

General: consider reviewing paper for minor typos, etc. to improve readability.

Response:
Thank you.

Abstract: "This study aims to examine the extent and nature..." It is not clear what this means, consider revising.

Response:
Extent refers to how widespread the use of GBTM is in adherence research and nature refers to how it is used, what questions it aims to answer, which is what this review aims to examine. These are broad terms which align with the purpose of scoping reviews-to describe the research area as opposed to in a systematic review which aims to answer a specific question. We have clarified that extent refers to the number or breadth of papers that use GBTM in medication research in the Objectives setting.

Introduction, end of paragraph 1: "... usually involving summary statistical estimates". This is unclear. Perhaps an example would help clarify.

Response:
Thank you, we have amended the end of this paragraph to the following: 'Summary adherence estimates include measures such as the proportion of days covered (PDC) and medication possession ratio (MPR), which are commonly used to describe adherence using administrative claims data.²

Introduction, paragraph 3: you state that GBTM has been used for the past 15 years. Are you sure this is accurate? I had thought Franklin et al. was the first to use GBTM for medication adherence in 2013, but the review you cite⁴ shows an earlier paper by Modi et al. in 2011 that used GBTM for medication adherence⁵. However, I do not see or know of any GBTM papers for medication adherence that were published before this.

Response:
Thank you for highlighting this. This is a general statement regarding the time period for which one gets publication hits in PubMed using the search strategy, but it not a definitive fact. As such we have modified the language here to say 'Over the past number of years...'. We hope the review will provide more insight into when GBTM was first used in adherence research because as you have stated, there is evidence to suggest use prior to Franklin's seminal paper in 2013(2).

Rationale: "mapping" and "scoping review" may be standard terminology for this type of review, but consider giving a clearer definition of these terms earlier in the paper. Readers of your final paper, specifically researchers who want to use GBTM for medication adherence projects, may not be familiar with these terminologies.

Response:
In the objective and aims section we state the following, which describes the purpose of the scoping review: 'The objective of this scoping review is to describe the nature, number, scope and methodology of published research articles using group-based trajectory

modelling....'. As per our response above, a scoping review is different to a systematic review in that it doesn't aim to answer a specific question.

Objective and aims: What do you mean by "nature" and "extent"?

Response:

As responded to above.

Methods, paragraph 1 and throughout. For stage (1), "identify the research question", I believe clarification is in order. May be difficult for reader to understand if this means research questions as it relates to your review, or the research questions of the papers you are reviewing.

Response:

The research question relates to the research question of the review, which is used to direct the search for studies, data extraction etc. We clearly state in the methods section that identification of the research question is the first stage in the scoping review process. To enhance clarity we have amended the 'identifying the research question' paragraph to state the following: 'The following research questions for the review were identified based on the aims of the review:'

Search strategy. I believe the search terms are fairly well-defined, but a table may help to better visualize all the possible combinations and how the Boolean operators are applied. Additionally, for medication adherence search terms, what about the terms "adherence" and "compliance", etc., without the word medication directly in front of it? Would you potentially be missing some papers who never explicitly said "medication adherence"? What about wildcards? E.g. adheren to capture adherence and adherent?*

Response:

We agree and we contemplated this. However, the current search strategy identified the papers we are aware of that use GBTM in medication adherence research, in addition to 1000's of other potentially relevant papers (total results>6000). However, as outlined in the previous response to reviewer 2, there is a trade-off between comprehensiveness of the search strategy (particularly when it comes to medication adherence studies) and the resources required to search through the additional 1000's of abstracts that broader terms can result in. In Scopus and Embase we have modified search terms including 'medication adherence' such that we obtain results that have medication and adherence in close proximity, but not necessarily together.

Charting the data: What about how medication adherence was modeled as a function of time? All cubic? All quadratic? A mixture of 0-order through quartic?6

Response:

Thank you for this suggestion, we agree this information would be useful to know. As such we have modified the data extraction section as follows: 'Information on the order used (cubic, quadratic etc) to model groups will be extracted, if available.'

Charting the data: It is unclear if this is mentioned elsewhere, but what about the purpose of the

GBTM. Are the groups meant to be an exposure, with associations with clinical outcomes the purpose? Are the adherence groups the outcome of the study, to understand patterns of adherence in normal practice or as part of an intervention to change adherence? Or are the groups meant to adjust for health-seeking behavior? Other potential purposes....

Response:

Thank you. Yes we agree and have stated the following in the charting the data section: 'Next, information on the study design will be collected including the aims/purpose of the study, whether adherence was modelled as an exposure, covariate or outcome....'

Conclusion: "The over-arching purpose..." Are these the only reasons to use GBTM for medication adherence studies? What about measuring medication adherence simply to observe what the behavior is? Or as a health-seeking behavior to adjust for the healthy user/sick stopper bias?

Response:

The most useful application of GBTM in adherence research, from our point of view as pharmacists, psychologists and adherence researchers, is the more precise identification of the groups of people who may benefit from adherence interventions and the stage of treatment at which intervention would be most beneficial. For researchers who lack the assistance of programming experts, the computational workload required to carry out GBTM is larger in comparison to calculation of summary statistics. We agree that is interesting to observe adherence behaviour using this methodology but if it doesn't provide additional insight over traditional metrics that can be actioned upon, the clinical relevance of its application is questionable. We hope the scoping review will help to provide some clarity on this.

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2. Franklin JM, Shrank WH, Pakes J, Sanf elix-Gimeno G, Matlin OS, Brennan TA, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Medical Care*. 2013;51(9):789-96.

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 June 2020

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Julie Lauffenburger 

Center for Healthcare Delivery Sciences, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Group-based trajectory modelling has been applied to the field of medication adherence since 2012, and as the authors point out, there has been heterogeneity in how the field has used these techniques. This is an interesting protocol, and the study, when completed, should provide insight to the field of medication adherence and the GBTM approaches.

To enhance their study, I have a few minor suggestions for the authors:

- In the inclusion criteria, please clarify what terms will be used for group-based trajectory modeling and medication adherence. Both have many synonyms in the literature, and it would be useful for replicability to know which terms the authors used. It is not clear as presented whether this is a completely exhaustive list of the terms used.
- The authors should also clarify which data sources for trajectory modeling are being used in the underlying studies, such as whether they are all done using pharmacy refill/claims data.
- While I am not aware of any RCT that has used GBTM in its modeling for adherence to date, I would not have excluded them outright. The authors should at a minimum provide how many studies were excluded because they were RCTs.
- Similarly, it would also be useful to classify whether GBTM has exclusively been used as the way of classifying adherence as an outcome, or whether it has been applied (and how it has been applied) as an exposure or covariate.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medication adherence, pragmatic trials, cardiometabolic disease, pharmacoepidemiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 25 Jul 2020

Caroline Walsh, Royal College of Surgeons in Ireland, Beaux Lane House, Lower Mercer's Street, Dublin 2, Ireland

In the inclusion criteria, please clarify what terms will be used for group-based trajectory modeling and medication adherence. Both have many synonyms in the literature, and it would be useful for replicability to know which terms the authors used. It is not clear as presented whether this is a completely exhaustive list of the terms used.

Response:

Thank you and we agree. We intend to publish the full search string used across all databases with the final manuscript. Given the numerous terms used for both medication adherence and group-based trajectory modelling it is unlikely that the list is completely exhaustive. However, initial searches have indicated >6000 search results for abstract screening from the current combined search strings across the databases. This search has identified well-known papers that have described the use of group-based trajectory modelling. In addition, we will be searching the reference lists of included texts in the review which should help to broaden the search.

The authors should also clarify which data sources for trajectory modeling are being used in the underlying studies, such as whether they are all done using pharmacy refill/claims data.

Response:

We agree this is an important piece of information to extract from the studies and have stated in the 'charting the data' section: 'Further, information specific to medication adherence measurement will be collected including the data source.'

We will not be using data source as a criteria for exclusion.

While I am not aware of any RCT that has used GBTM in its modeling for adherence to date, I would not have excluded them outright. The authors should at a minimum provide how many studies were excluded because they were RCTs.

Response

Thank you for this suggestion and upon reflection we agree. However, it is important to note that the study abstract would need to state that some form of longitudinal (GBTM, latent class, patterns) analysis on the basis of adherence behaviour was performed in order to be included. As such we have amended the inclusion criteria as follows: 'Randomised controlled trials will be included if it specified in the study abstract that longitudinal analysis of adherence was performed as part of the study.'

Similarly, it would also be useful to classify whether GBTM has exclusively been used as the way of classifying adherence as an outcome, or whether it has been applied (and how it has been applied) as an exposure or covariate.

Response:

It must be stated in the abstract that GBTM (or some variant) has been used to model medication adherence, otherwise it would not be possible to complete the review efficiently.

To ensure this is communicated clearly, we have amended the inclusion criteria to the following: 'Furthermore, publications will have to include in their abstract...'
We agree regarding the use of GBTM and have amended the 'charting the data' section to include the following: '. Next, information on the study design....., whether adherence was modelled as an exposure, covariate or outcome,'

Competing Interests: No competing interests were disclosed.

Reviewer Report 29 May 2020

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Hannah Durand 

School of Psychology, National University of Ireland, Galway, Ireland

This article outlines the protocol for a scoping review of group-based trajectory modelling (GBTM) in medication adherence research. This review will make an important contribution to the literature given the vital shift in focus towards longitudinal adherence research that better accounts for variance in patient adherence behaviour over time and disease trajectory. I look forward to seeing the results of this work.

The authors present a clear rationale for the review. Given the rapid increase in the use of GBTM in this area, this review is timely and well-justified. The protocol is well-written, clear, and detailed. The authors clearly outline the study objectives, specifically to describe the nature, number, scope, and methodology of published research articles using GBTM to measure medication adherence and to identify future research needs.

The authors propose a scoping review methodology given the broadness of the research question/aims and the considerable heterogeneity of medication adherence research with regard to measurement of adherence behaviour. This measurement heterogeneity is a vitally important consideration in any synthesis of adherence research. This approach to synthesising this particular body of evidence is appropriate. The authors utilise best-practice guidelines for the conduct and reporting of scoping reviews (e.g., Joanna Briggs Institute, 2019; Tricco *et al.*, 2018).

The authors provide sufficient detail on the inclusion and exclusion criteria; the search strategy including databases to be screened, the search string to be used, and details of citation search; the screening procedure; data charting; and on collating, summarising and reporting of results to allow replication.

Additional minor comment:

In line 1 of the abstract, abbreviation GBTM should appear after the word 'modelling'.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medication adherence; quantitative methods; evidence synthesis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 25 Jul 2020

Caroline Walsh, Royal College of Surgeons in Ireland, Beaux Lane House, Lower Mercer's Street, Dublin 2, Ireland

We would like to thank the reviewer for reading the manuscript and providing critical analysis. We have updated the manuscript to incorporate the abbreviation suggestion.

Competing Interests: No competing interests were disclosed.
