

A NEW METHODOLOGY FOR CREATING AND ANALYSING COMPLEX INTERVENTIONS

Abstract

Clinical researches and complex research interventions are the present interventions which need critical care examination and thorough statistical evidence. There is a need to enroll even the clinical trial data that reflects the most efficient data reflection to the conventional literature support. Thus there are very less reports and intervention methodologies that support the use and recreation of complex analytical approach to sort the data. This review presents a new way of approach that can analyze, predict and define the complex research data to simplified and stratified way. The successful research based approach includes implementation of clinical trial data and also evidence based trial data to be integration for compilation and statistical representation of the data with full integrity. Analyzing the pit falls with the GAP analysis and reporting the meta data is effective to sort the complex research protocol.

Keywords: Research; Clinical Trial; Integrity; Statistics; GAP analysis

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I. INTRODUCTION

Modern health care systems and infrastructure must include clinical trials [1,2]. Enrolling in a clinical trial is sometimes regarded as the best course of treatment [1] for instance a cancer patient since it advances knowledge and improves care, which benefits society and individuals. In light of this, clinical trials get annual investments in the billions of dollars, with approximately \$10 billion going to oncology trials alone [3]. Attempts to improve clinical trials haven't yet resulted in appreciable increases in enrolment and completion rates for ongoing studies, nor have they helped us learn more about how to run new trials more effectively [4]. In other words, clinical trials provide substantial evidence-based social and personal benefits, yet implementation problems still exist [5]. Suggesting a novel strategy and also integrating implementation research into the setting of clinical trials [6], in order to close gaps in the successful implementation of trials, we see researching clinical trials [7] as sophisticated evidence-based interventions, frequently with subpar execution [8]. The discipline focuses on applying interventions with established advantages and bridging the "evidence to practice gap" between the theoretical and practical benefits of interventions, such as those found in clinical studies [9]. Implementation science's central problem is how to translate benefits [10]. The difficulty of implementing such programs is partially due to the multiple levels, components, processes, and stakeholders involved in a research program, referred to as a complex intervention [11].

II. CONSIDERING CLINICAL TRIALS AS COMPLEX INTERVENTIONS

Clinical trials [12] can also be regarded as complex interventions because they involve different parties, activities, and elements operating at various levels. Through the participation of participants in the protocol administration of particular interventions, a clinical trial seeks to enhance health [13].

Complex interventions [14] are frequently employed in public health practice, health and social care services, and other areas of social and economic policy that have an impact on health [15]. These interventions are implemented and assessed on a range of scales, from the individual to the social [16]. Examples include the development of a novel surgical technique, the redesign of a healthcare programme, and a modification to welfare laws [17]. In 2000, the UK Medical Research Council (MRC) published a framework for scientists and research funders on creating and assessing complex interventions [18]. In 2006, the MRC updated its advice [19]. Although these texts are still in widespread use and are now supported by a variety of more in-depth guidelines on particular elements of the research process [20,21], 4-8 several significant conceptual, methodological, and theoretical advancements have occurred since 2006 [22].

These advancements have been incorporated into a new framework that the National Institute of Health [23] has ordered NIHR research and the MRC. The framework seeks to assist researchers in their collaboration [24] with other stakeholders in identifying the main questions about complicated interventions and in designing and carrying out research with a variety of viewpoints and the proper selection of techniques [25,26].

Guidelines for creating and assessing complex interventions from the UK Medical Research Council are widely used [27]. And it has been replaced by a new framework that

was commissioned jointly by the Medical Research Council and the National Institute for Health Research [28]. This framework takes into account current theory and methodological advancements as well as the requirement to maximize the effectiveness, utility, and impact of research [29].

III. FRAMEWORK FOR CREATING AND EVALUATING COMPLEX INTERVENTIONS DEVELOPMENT:

The result of a process that has four steps is the revised Framework for Developing and Evaluating Complex Interventions [30]:

A public consultation on a draught of the framework was held in April 2019, and participants were invited to submit written comments in response to advertisements [31,32] posted on social media, email lists, and other networks (52 detailed responses were received from stakeholders).

1. A gap analysis to identify advancements in methods and practice since the publication of the previous framework [33]
2. In May 2018, 36 participants participated in a full-day expert workshop to explore the themes identified in the gap analysis [34].
Redraft utilising the information from the earlier phases, then have a final expert review.
3. The MRC Population Health Sciences Group published its findings in March 2020 after the MRC-NIHR Methodology Research Programme [35-37] Advisory Group reviewed and approved the framework and before it underwent additional external peer and editorial assessment via the NIHR Journals Library peer review procedure.

IV. COMPLEX INTERVENTIONS – WHAT ARE THEY?

A complicated intervention might be one that involves multiple components, including: The range of behaviours targeted [38-42], the number of groups, contexts, or levels targeted, the number of intervention components involved, the number of components allowed to be flexible, the experience and abilities needed by individuals giving and receiving the intervention, etc. For instance, the Links Worker Programme was a primary care initiative in Glasgow, Scotland, that attempted to connect people with neighborhood services to support their ability to "live well" there. It focused on the individual [43], primary care (general practitioner (GP) surgeries), and community levels. The intervention was adaptable because it might be different at different primary care GP offices [44]. The Link Workers also provided assistance with a variety of health and wellbeing issues, including deprivation, substance abuse, and others. There were issues with use, employment, and learning [45]. The evaluation of this intervention was complicated, which affected several elements, including [46] the selection of relevant outcomes and assessment methods.

To allow for variety in the way, where [47], and by whom interventions are given, flexibility in intervention delivery and adherence may be allowed and received. Intervention standardization [48] may have more to do with the intervention's core procedures and purposes than it does with the precise arrangement of its given elements. For instance, procedures for surgical trials can be created with flexibility for intervention delivery [49].

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Interventions [50] involve a theoretical deconstruction into components, followed by agreement on variations in how those components are delivered that are allowed and not allowed. With this method, a complex intervention can be implemented differently in various circumstances while preserving the integrity of its essential elements.

The value of identifying [51] mechanisms is emphasized by the significance of interactions between the intervention and its surroundings, where the causal connections are the mechanisms of change between the elements of an intervention and the results and outside variables that influence and mould whether and how results are produced [52].

V. VIEWPOINTS ON RESEARCH

The prior framework and recommendations were based on a paradigm where the crucial question was to determine whether an intervention [53] was successful. Complex intervention research that is mainly motivated by the interventions that could be provided by this query might implementable, affordable, transferrable [54], and scalable.

The development, identification, and evaluation of entire system [55] interventions as well as the evaluation of how interventions contribute to system change must be included in the scope of complex intervention research in order to be consistent with a broader definition of complexity [56].

A viewpoint on efficacy or effectiveness has been used in the majority of complicated health intervention research to date, and for some research topics these perspectives will continue to be the best choice [57]. Even though some equally important inquiries for the decision-making process makers cannot be resolved by research limitations to a perspective of efficacy or effectiveness. a bigger variety and synthesis of research viewpoints, strategies that address issues beyond effectiveness and efficacy, researchers must use these methods backed by sponsors [58]. This will facilitate improvement. How important decision-making questions are but complex intervention research can provide an answer [59].

Examples of questions are:

1. Will the results shown in the experiment be replicated when this successful intervention is used here?
2. Is the intervention financially viable?
3. What are the most crucial tasks that we must complete? that will enhance health outcomes as a whole?
4. When there is no proof from randomised trials and the impossibility of holding a trial of this nature, what does the evidence currently available [60] indicate is the best option right now, and how might this be assessed?
5. What broader changes will result from this intervention?
6. How are the effects of the intervention mediated by various contexts and settings

VI. COMPLEX INTERVENTION RESEARCH PHASES AND FUNDAMENTAL COMPONENTS

Research on complex interventions is divided by the framework into four stages [61]:

Identification or development, feasibility, assessment, and effective implementation depending on the main uncertainty [62] surrounding the relevant intervention, a study programme may start at any stage. If there are uncertainties, phase repetition is better than automatic advancement lingers unresolved. Each stage [63] includes a standard set of essential components—taking context into account, developing and programme theory refinement, stakeholder engagement, recognising important unknowns, modifying the intervention, as well as financial factors. The early consideration these components and frequent review are required during the entire research process, but particularly prior to transitioning between stages (for instance, between testing and assessment of viability).

1. Core components:



Figure 1: Analyzing the research cycle

- 2. Context:** A complex intervention's [Figure 1] outcomes may frequently be very context-dependent, meaning that an intervention that works well in one situation might not work as well or even be detrimental in another.

The examples in table 1 demonstrate how interventions can alter the contexts in which they are used, elicit responses from other agents, or alter behavioural norms or exposure to risk, changing the contexts in which they are implemented and causing changes in the effects that are experienced over time. It is possible to think of context as dynamic and multidimensional. The healthcare, health system, or public health environments in which interventions are implemented all have important physical, geographical, organizational, social, cultural, or political characteristics [Table 1].

Table 1: Complex adaptive system characteristics and illustrations

Characteristics	Example
EMERGENCE: Emergent, frequently unexpected qualities that are characteristics of the entire system are a property of complex systems.	The creation of new social interactions inside the group that enhance members exposure to risky behaviours while diminishing their contact with other young people who are less tolerant of risk taking could undermine group-based therapies that are aimed at young people at risk.
FEEDBACK: where one alteration strengthens, advances, equalises, or weakens another	A smoking ban in public areas lowers smoking's visibility and convenience, which in turn discourages youth from starting to smoke, further lowering smoking's visibility in a positive feedback loop.
ADAPTATION: alteration in system behaviour following an intervention	Retailers resorted to the prohibition on multi-buy discounts by offering individual alcohol items at a discount and at the same price as they would have been if they had been a part of a multi-buy offer.
SELF-ORGANISATION: order resulting from local interactions rather than from a predetermined plan or outside control	Alcoholics Anonymous was founded by recovering drinkers who self-organized after realising that some social components of alcohol dependence were not addressed by individual treatment.

VII. PROGRAMME THEORY

Programme theory explains [63] how and under what circumstances an intervention is anticipated to produce its effects. It describes the intervention's main elements and how they interact, its mechanisms [64], the aspects of the context that are anticipated to affect it, and how those processes might affect the environment. Programme theory can be used to highlight major ambiguities and research [65] problems, as well as to encourage shared understanding of the intervention among many stakeholders. Researchers still need to theorize an intervention (like a policy) that has been produced by others before attempting to analyse it.

The best method is to construct the [66] programme theory from the outset of the research project, involving a variety of stakeholders, and basing it on theory and evidence from related fields, and to improve it over time. The EPOCH experiment examined a significant quality programme of improvement focused towards 90-day rates of patient survival after emergency abdominal surgery, complete with a clearly described programme theory, which at first backed the adaptation of programme delivery to local circumstances. The creation, application, and analysis, considering the programme idea in reverse led to recommended modifications for the installation of the programme for quality improvement [65].

When a theory-based viewpoint is used, an improved programme theory is the main goal and an important evaluation outcome. Improved transferability will benefit from programme theory. Various actions in various settings and aid in creating evidence and comprehension that aid in decision-making manufacturers. In addition to a complete programme articulation, It can assist in supplying visual representations [56-60]—for using a realism matrix, a logic model, or a system map, offering options based on which is most suitable from the point of view of the research and research issues. Despite being helpful, a single picture representation is not likely to adequately express the Program theory should be stated clearly at all times well within the published, reported, and other financing requests.

VIII. STAKE HOLDERS

Individuals targeted by the intervention or policy, those involved in its creation or implementation, or those whose personal interests are whether personal or professional interests are impacted [54,58] (all those who are interested in the subject). Public and patients are important players. Meaningful interaction with the right parties at each stage of the research is required to fully realize the development's potential or selecting a strategy that will likely have beneficial effects on health and to improve prospects for bringing about changes in practise or policy [56,57]. For instance, involvement of patients and the public activities in the PARADES programme, which assessed methods to lessen harm and enhance people's results were extensive and central in those with bipolar illness to the undertaking.

Participating service users who had firsthand knowledge of bipolar disorder offered various advantages, such as improving the intervention but also enhanced distribution and evaluation techniques. Additionally, the study's service consumers reported good results, such as more stable employment and advancement to higher education. Broad-mindedness and Consultation is required to pinpoint a variety of the proper parties. Stakeholder participation will serve different purposes [54-59] depending on the situation and stage of the investigation, but is crucial for determining the order of research questions, the co-creation of the programme theory, selection of most beneficial research angle, as well as overcoming Implementation and evaluation are practical challenges. Despite this, researchers need to be aware of potential conflicts of transparency and utilization among stakeholders, a system for identifying potential conflicts of interest [53,54].

Stakeholder priorities should be elicited through research, but it should also take into account that why they are the priorities. Given careful thought of the suitability and identification techniques and relevant stakeholders participation is required [52,54].

IX. IMPORTANT QUESTIONS

At each stage of the study process, several questions could be resolved. A flexible and emergent method must be provided in the research design and execution to explore the numerous uncertainties present [56,59]. Therefore, given what is currently known and what the research team and stakeholders select as being most important to determine, researchers should take their time constructing the programme theory, clearly defining the remaining uncertainties. The formulation of research questions, which in turn determines the choice of research perspective, is guided by judgments about the major uncertainties [52,53].

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Trials evaluating the effectiveness of relatively simple therapies under strictly controlled Circumstances [34,54], where research questions may be answered with high assurance will always be crucial but interpreting the evidence about the various contexts of daily behaviour is frequently very challenging [36,45]. In terms of intervention research in public health and healthcare environments to undertake greater priority, tougher evaluation questions should be given to theory-based, blended techniques, or evaluation of systems that takes complexity and it places a focus on system, context, and implementation. This strategy might facilitate greater comprehension [36,38] and pinpoint crucial decision-related implications makers, though with qualifications, presumptions, and limitations.

Instead of continuing the established trend to prioritize strong research designs that answer some questions with certainty but are unsuited to resolve many crucial evaluation questions, this more inclusive, deliberative process could place more value on ambiguous findings that nonetheless inform crucial decisions where evidence is lacking [23,25].

X. ENHANCING THE INTERVENTION

The complexity of the intervention may need to be increased at each step of the complex intervention research as well as when moving from one phase to another [46,46], depending on the data gathered or the evolution of the programme theory. Engaging potential intervention users to help inform improvements can increase the viability and acceptability of therapies. An online physical activity planner, for instance, was discovered to be challenging to use [47,48], because of the tool's incorrectly personalised recommendations. A number of planner versions were created using interviews and observations to enhance usability and the advice offered. Through this iterative method, the planner was improved and now exhibits more viability and accuracy [48].

The programme theory should serve as a guide for refinements, and appropriate boundaries should be agreed [54,58] upon and established at the start of each research phase and changes should also be transparently justified. The policy or practise context may also place restrictions on the [59,62] scope for refinement. In the efficacy and effectiveness research evaluation phase, when interventions should ideally not change or evolve throughout the study, refinement will be infrequent. Refining interventions in response to accumulated data or as an adaptive and variable response to context and system change, however, are likely to be desirable features of the intervention and a key focus of the research between the phases of research and within systems and theory-based evaluation studies.

XI. MONETARY CONSIDERATIONS

Economic evaluation, which is the comparative analysis of various courses of action in terms of both costs (resource consumption) and outcomes, should be included in all stages of intervention research (outcomes, effects). Early involvement of economic experts will help in identifying the range of costs and benefits to consider in order addressing [65] the issues that matter most to decision-makers. Broader approaches, like cost benefit analysis or cost consequence analysis, which aim to capture the full range of health and non-health costs and benefits across different sectors, will frequently be more appropriate than more narrow [66] approaches, like cost effectiveness or cost utility analysis for an economic evaluation of a complex intervention.

- 1. Phases:** Constructing or locating a complex intervention. The term "development" describes the entire process of creating [64] and organising an intervention from its initial conception to any feasibility, pilot, or assessment studies [67]. There has lately been guidance on intervention development, but we want to emphasize that complex intervention research doesn't usually start with brand-new or researcher-led interventions [24,28].

For instance:

- An intervention that has been produced elsewhere and has the potential to be modified for a new environment may be a significant source for the development of an intervention [36].
 - Existing interventions may be modified to better suit a new demographic, a different environment, or alternative goals (eg, a smoking prevention intervention being adapted to tackle [35] substance misuse and sexual health). A well-developed programme theory can assist in determining which aspects of the preceding intervention(s) need to be modified for various applications as well as the crucial mechanisms that should be kept even if implemented slightly different.
 - Evaluation research [37] places a lot of emphasis on initiatives that are led by policy or practice.
 - Again, identifying significant [38] uncertainties and figuring out how the intervention might be evaluated require exposing the implicit theoretical underpinnings of an intervention and creating a programme theory. Although the rollout has already begun, this phase is essential because it aids in the identification of the change mechanisms, relevant contextual factors, and applicable outcome measures [39].
- 2. Feasibility:** To assess predetermined progression criteria for the evaluation design (such as reducing uncertainty around recruitment, data collection, retention, results, and analysis) or the intervention itself, a feasibility study should be developed (eg, around optimal content and delivery, acceptability, adherence, likelihood of cost effectiveness, or capacity of providers to deliver the intervention) [40].

These queries should be taken into account if the programme theory implies that contextual or implementation issues may have [41] an impact on the acceptability, efficacy, or cost-effectiveness of the intervention. Despite being disregarded or hurried in the past, the need of feasibility testing is now widely acknowledged [42] with clear definitions of key terms and ideas. Researchers should think about performing [43] an evaluability evaluation to establish whether and how an intervention can be productively evaluated before starting a feasibility study. In order to agree on the intended outcomes of the intervention, the data that may be gathered to assess processes and outcomes, and the possibilities for creating the evaluation, stakeholders must collaborate in the evaluation of assessment process [46]. The ultimate result is a recommendation on whether or not an evaluation is viable, if so, how to go about doing it and at what cost. Economic modelling can be done during the feasibility stage to determine whether it is worthwhile to move forward with a full-scale evaluation and to determine whether the anticipated benefits of the intervention will likely outweigh the expenses (including the cost of additional research). Before beginning a full-scale evaluation, additional work may be needed to gradually improve the intervention based on the findings of the feasibility study [48].

XII. ASSESSMENT

The new framework defines evaluation as addressing a wider range of issues, such as determining what other effects an intervention has, theorizing how it functions taking into account how it interacts with the context in which it is implemented, considering how it contributes to system change and considering how the evidence can be used to support decision making in the real world [40-50]. This suggests a change in emphasis from getting objective estimates of efficacy to prioritizing the usefulness of information for decision-making when choosing the best research perspective and when prioritizing relevant research questions [51].

The selection of outcome measures or evidence of change is an essential component of evaluation design. In order to determine which outcomes are most crucial and how to handle various outcomes in the analysis while taking statistical power and open reporting into account, evaluators [52] should consult with stakeholders. It may not always be acceptable to draw a clear line between one core result and multiple secondary outcomes, especially when the programme [53] theory indicates implications across a variety of areas. Predetermined subgroup analyses should be conducted as needed to support the research questions and reported. Even if such [54] analyses are weak, they should be included in the procedure since they can be valuable [55] for formulating hypotheses to test in additional research or for use in meta-analyses that [56] come after them. Instead of tracking changes in people, outcome measurements might record changes in a system. Examples include the adoption of policies, modifications to social [57] standards, or the normalization of practice. Another example is the alteration of connections [58] inside an organization. Such system-level effects include how shifting a system's dynamics affects behaviors in other system components such as the possibility of [60] smoking in the home after a public smoking ban.

There are a variety of study designs available to researchers, and each design is best suited to take into account a particular situation [21-24] and a particular research issue. Adaptive designs, SMART trials (sequential multiple assignment randomised trials), n-of-1 trials, and hybrid effectiveness-implementation designs are major areas of technique development to increase the effectiveness of complicated intervention studies. If a randomised design is not feasible, as might be the case in natural experiments or system evaluations, non-randomized designs and modelling methodologies may work best. In complicated intervention research, where qualitative and [25] mixed methods designs may be required to provide answers to problems beyond efficacy, a purely quantitative strategy, using an experimental design without any extra [36] components like a process evaluation, is rarely sufficient.

Questions about implementation fidelity and quality (such as what is implemented and how), change mechanisms (such as how does the given intervention cause change?), and context (such as how does context affect implementation and outcomes?) can all be addressed through process assessment. Process analysis can assist identify why an intervention works and how it might be improved, or why it unexpectedly fails or has unintended consequences. These results can help the intervention programme theory be developed further. It is not always as easy to distinguish between process and outcome evaluation in a theory-based or systems evaluation as it is in effective research [28].

These viewpoints could give theory development a higher priority than evidence generation and employ case study or simulation techniques to comprehend how outcomes or system behaviour are produced as a result of action [27].

XIII. IMPLEMENTATION

Early implementation planning increases the likelihood of creating an intervention that can be successfully implemented and sustained in real-world contexts. The intervention programme theory should anticipate implementation concerns, and these concerns should be taken into account during the phases [23-25] of intervention formulation, feasibility testing, process analysis, and outcome analysis. The implementation of strategic components and contextual elements that facilitate [28] or obstruct the realization of impacts, in addition to implementation-specific outcomes (such as reach or uptake of services), are crucial in research. Given that the basic goals of the programme are upheld and the modifications made are well known, some flexibility in the way interventions are implemented may facilitate intervention transferability into various contexts (a crucial component of long-term adaptation) [29].

Researchers took into account implementation at each stage of the ASSIST project, a peer-led, school-based intervention for smoking prevention. The intervention was created with the intention of causing the least amount of disruption to school resources; the feasibility study led to the intervention being improved to increase acceptability and reach to male students; and in the evaluation (cluster randomised controlled trial), the intervention was delivered as closely [30] to real world implementation as possible. An intervention manual that identified crucial elements and other elements that could be modified or eliminated to allow for flexible implementation while achieving delivery of the key mechanisms of change was included in the implementation. Additionally, a training manual for the trainers and ongoing quality assurance built into rollout for the longer term were included [34]. Evaluation occurs during or following the implementation of the intervention in a real-world setting in natural experimental research. In order to shorten the time to translate effectiveness research into common practice, highly pragmatic effective trials or certain hybrid effective implementation designs also combine effectiveness and implementation outcomes in one study. Economic factors should be taken into account while developing an intervention and investigation in the early phases. Decision maker's willingness and ability to act on the findings of economic analyses can be influenced by how the findings are communicated and presented to them [35].

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