Administration and Policy in Mental Health and Mental Health Services Research (2022) 49:1084–1094
https://doi.org/10.1007/s10488-022-01218-x

COMMENTARY

Precision Implementation: An Approach to Mechanism Testing in Implementation Research

Hannah E. Frank[1,2] · **Joshua Kemp**[1,2] · **Kristen G. Benito**[1,2] · **Jennifer B. Freeman**[1,2]

Accepted: 18 August 2022 / Published online: 27 September 2022

Abstract
Advancing mechanism-focused research in implementation science is a priority given its potential to improve tailoring and efficiency of implementation strategies. Experimental therapeutics, or experimental medicine, offers an approach for mechanism testing that has been promoted by the NIH Science of Behavior Change and endorsed by the National Institute for Mental Health. This approach has been applied across the translational spectrum – with initial applications to biological research and more recent applications to psychosocial treatment development research. We describe further advancement of experimental therapeutics along the translational spectrum and describe how it is ideally suited to inform precision experimental tests of implementation strategy mechanisms, which we term *precision implementation*. Such an approach to mechanism testing will allow for identification of causal dose-response relationships between implementation strategies, presumed mechanisms, and implementation outcomes. We discuss the tension between the scientific rigor required to conduct mechanism-focused research using experimental therapeutics and the "real world" conditions in which implementation research takes place. We provide a series of example studies that show "beginning to end" application of this framework in research focused on provider implementation of an evidence-based intervention in routine clinical care settings.

Keywords mechanisms · implementation strategies · experimental therapeutics

Background: Why Study Mechanisms and What Makes it Challenging?

Advancements in implementation science have resulted in a proliferation of studies testing whether implementation strategies (Powell et al., 2015) lead to changes in implementation outcomes of interest (Proctor et al., 2011). However, a dearth of research has examined the mechanisms underlying implementation strategies, or *why* and *how* these strategies operate. Mechanisms in implementation science are defined as "the processes or events through which an implementation strategy operates to affect desired implementation outcomes" (Lewis et al., 2018, p. 3). A limited understanding of implementation strategy mechanisms prevents conclusions about the specific function and effect of each strategy (Alexander & Hearld, 2012). In recognition of this problem, increasing calls have been made for mechanisms to be more rigorously assessed in implementation science (Lewis et al., 2018, 2020; Michie et al., 2009; Powell et al., 2019; Williams, 2016). Precise measurement of theorized mechanisms will improve the field's understanding of how implementation strategies work (French et al., 2012), which in turn will improve our ability to select and tailor strategies for diverse settings and stakeholders (Powell et al., 2017). Without such efforts, we are left with little knowledge about the functional relationship between implementation strategies, implementation outcomes, and their mechanisms.

Studying mechanisms in implementation science is particularly challenging because of the complexity of settings in which implementation efforts take place. As described by Williams (2016), implementation strategies are likely to target multiple levels, such as individuals, organizations, and communities, which necessitates consideration of complex

✉ Hannah E. Frank
hannah_frank@brown.edu

[1] Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, 700 Butler Drive, 02906 Providence, RI, USA

[2] Bradley Hospital, Lifespan Health System, 1011 Veterans Memorial Parkway, 02915 Riverside, RI, USA

interacting factors. At the same time, mechanisms require a high level of specificity in their definitions, including a description of exactly how and when change takes place (Kazdin, 2007; Williams, 2016). As described by Lewis and colleagues (2020), Kazdin (2007) calls for at least seven criteria for establishing mechanisms, including (a) strong associations (between intervention and mediator AND between mediator and outcome); (b) specificity; (c) consistency; (d) experimental manipulation; (e) timeline (i.e. causes/mediators must temporally precede effects and outcomes); (f) gradient (i.e., dose-response relation); and (g) plausibility or coherence. However, no implementation studies have met all these criteria (Lewis et al., 2020). Few studies have conducted experimental manipulation of mechanisms and only one study has examined a dose-response relationship between mediators and outcomes (Lewis et al., 2020).

One approach that has promise to advance the research on mechanisms in implementation science is a *precision implementation* approach. This term refers to the process of identifying mechanisms of expected change when conducting implementation efforts to assess why and how implementation strategies work or fail. Conducting precision experimental tests of mechanisms engaged by implementation strategies has the potential to inform the selection of strategies within a given context and to enhance our ability to generalize strategies to other contexts. Furthermore, identifying and rigorously measuring mechanisms may allow researchers to identify early indications of whether a change is happening as theorized, and then to engage in quick retooling and retesting (i.e., "fast-fail"; Grabb et al., 2020; Lyon et al., 2020; Lyon & Koerner, 2016), which will in turn increase the efficiency of implementation science. With calls for the pairing of implementation science with precision medicine (Chambers et al., 2016; Chanfreau-Coffinier et al., 2019), it is appropriate to begin focusing on the development of methods and measures for evaluating the mechanisms of implementation strategy effects in the process of implementation. We discuss the application of an experimental therapeutics approach, which we are terming *precision implementation*, as one step toward addressing the need for rigorous, precision testing of mechanisms within implementation science. While a precision approach to applying implementation strategies may be aspirational at this early stage, routine deployment of these methods has the potential to lead to significant advancements in our understanding of implementation mechanisms.

Experimental therapeutics has been advanced by the NIH Science of Behavior Change (Nielsen et al., 2018) and the National Institute of Mental Health (NIMH; Insel 2015; Insel & Gogtay, 2014) to support precision testing of mechanisms in clinical trials. Experimental therapeutics, also referred to as experimental medicine (Nielsen et al., 2018), calls for the demonstration of "target" (i.e., mechanism of action) engagement and an illustration of its effect on an outcome. Experimental therapeutics has been historically associated with biological interventions and viewed as less relevant to interventions at the psychosocial level. This can be attributed to experimental therapeutics' origins in medical research and efforts by the NIMH to connect experimental therapeutics to its biologically-oriented Research Domain Criteria (RDoC) initiative (Insel, 2015). However, experimental therapeutics should theoretically be as applicable to psychosocial treatment and implementation research as it is to biological research (Insel & Gogtay, 2014). Indeed, it has been increasingly adopted to understand mechanisms of change in psychosocial research (e.g., Lewandowski et al., 2018), but experimental therapeutics has not yet been widely advanced further along the translational spectrum to implementation science. The aim of this paper is to describe how experimental therapeutics can be applied to advance the study of mechanisms within implementation science.

The Experimental Therapeutics Approach

Experimental therapeutics is a set of principles that guides the advancement of mechanism-informed research. Precise testing of theorized mechanisms of change during an intervention (i.e., treatment or implementation strategy) allows researchers to understand the causal pathways through which intended outcomes occur. Equally as important, these methods can help clarify why an intervention fails to produce an intended outcome (Geng et al., 2022). Rather than focusing on whether an intervention leads to changes in distal outcomes (e.g., symptomatology in an effectiveness study; adoption in an implementation study), experimental therapeutics requires the identification of a modifiable *target* that, when engaged or changed by an intervention, leads to a change in the more distal outcomes. Targets are defined a priori and experimental studies are conducted, which allows for precise testing of putative mechanisms. As noted by Raghavan and colleagues (2019), targets can span a wide range of constructs and can be biological, cognitive, affective, behavioral, social, or interpersonal. Importantly, this requires a shift to thinking *first* about target engagement (dark gray box in Fig. 1) and *second* about clinical or implementation outcomes (light gray box in Fig. 1; Lewandowski et al., 2018).

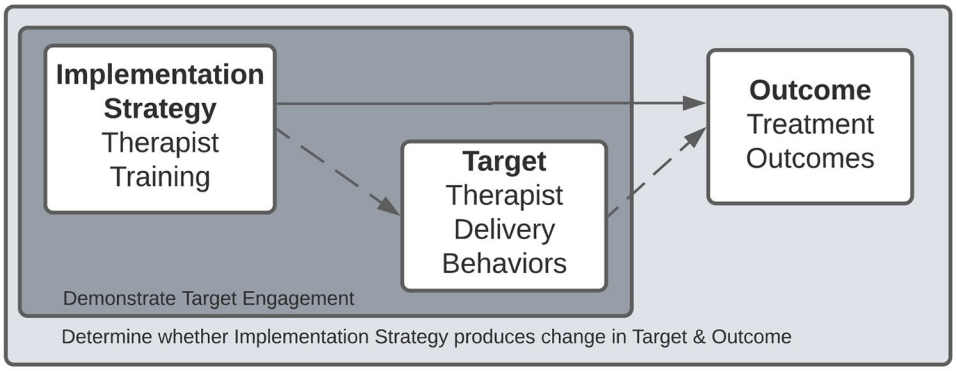

Fig. 1 Experimental therapeutics mechanism testing framework

Applying Experimental Therapeutics to Implementation Science

Although there is ultimately a need to assess implementation outcomes and to understand the multi-level factors that influence these outcomes (Williams, 2016), it is also important to establish direct causal, dose-response relationships between implementation strategies, presumed mechanisms, and implementation outcomes. There are several potential benefits to this approach. First, it is likely that data gathered about specific theorized implementation strategy mechanisms will yield practical information that can be applied by individuals in several settings. Second, manipulating a small set of carefully designed mechanisms along a causal pathway can take place in complex settings. Combining the assessment of contextual factors with manipulation of a narrow set of potential mechanisms in this way will contribute to future work focused on assessment of multi-level mechanisms and moderators. Third, given the limitations to measurement within implementation science (Mettert et al., 2020; Powell et al., 2021), initially assessing specific, linear mechanisms will rely on fewer measures and a better understanding of dose. Over time, this assessment of individual mechanisms will contribute to an evidence-base of well-articulated mechanisms that can then be combined and tested for their additive effects. Finally, developing a thorough understanding of individual mechanisms will increase efficiency by improving our ability to select appropriate implementation strategies to target a given problem. Ultimately, the goal of precision testing of mechanisms will be to inform more complex, multi-level mechanistic research as it unfolds in usual care settings.

Steps for Using Experimental Therapeutics to Assess Implementation Mechanisms

In the following section, we describe the specific steps involved in the experimental therapeutics approach to assessing mechanisms. Importantly, this approach is consistent with other causal models that have been proposed for examining mechanisms within the context of implementation science (e.g., Lewis et al., 2018). However, a precision implementation approach to mechanism testing includes a particular emphasis on initial testing of target engagement before proceeding to assessment of additional outcomes.

Step 1: Identify a putative mechanism/target: For each implementation strategy being tested, a potential mechanism or "target" should be identified. Ideally, existing research will inform selection of putative mechanisms. For instance, the implementation strategy "remind clinicians" (Powell et al., 2015) is likely to lead to behavior change by increasing recall or memory of the desired behavior. Thus, an identified target is clinician memory. However, for implementation strategies that are novel or have a dearth of existing research on potential mechanisms, there may be a need for qualitative formative research to identify mechanisms to test (Raghavan et al., 2019). In some cases, it may be worthwhile to test more than one target in separate causal pathways if there are multiple candidate targets that may explain the relationship between the strategy and the outcome. Ideally, targets should be robust, have a strong empirical basis, and have some evidence of being linked to outcomes.

Step 2: Select and/or design an intervention: The next step in the experimental therapeutics approach is to select or design an intervention that is intended to make a change to the selected target. In the context of implementation science, this is likely to be an implementation strategy selected from among the 73 strategies identified via the Expert Recommendations for Implementing Change (ERIC) study (Powell et al., 2015), but may also be a novel strategy developed to specifically target the proposed mechanism. In a precision testing approach, it is especially important to adhere to

reporting guidelines for implementation strategies (Proctor et al., 2013; Rudd et al., 2020) to ensure that assessment of factors such as temporality and dose are considered in analyses.

Of note, there are times in which it is appropriate for Steps 1 and 2 to be reversed. In many cases, it is appropriate to begin with a mechanism that has a strong theory of potential causality (e.g., low self-efficacy being linked with less use of new interventions; Step 1) and then identify an implementation strategy that might address it (Step 2). In other cases, it might make sense to do the reverse and start with an implementation strategy that has strong research support (e.g., audit and feedback; Colquhoun et al., 2013; Step 2) and then identify a theoretically relevant mechanism that it might engage (e.g., increasing self-efficacy; Ivers et al., 2014; Step 1).

Step 3: Demonstrate target engagement: In this step, the primary focus of research is on assessing the relationship between the implementation strategy and the target *without* yet focusing on the implementation outcome. The research questions corresponding to this step are: (a) *Does your implementation strategy move the target?*; (b) *Is there a dose-response relationship between the implementation strategy and the target?*; and (c) *Is there* target specificity, *such that the intervention* only *leads to a change in what it is intended to move?* These questions can be assessed in the context of a go/no-go pilot trial. If the answer is "no" to any of these questions, it suggests a need to refine the implementation strategy or re-evaluate the hypothesized link between the implementation strategy, target, and outcome. If the answer is "yes" to all of these questions, that provides evidence for a causal relationship between the implementation strategy and the target. Furthermore, it ensures that any future effects on distal implementation outcomes might be primarily explained by a change in this specific target. As stated above, establishing a link between an implementation strategy and a target is the first step, which can then support research that examines relationships between the strategy, target, and outcome. The goal of this approach of demonstrating target engagement *first* is to confirm that a relevant mechanism is being targeted. An initial probe of a potential target uses fewer resources than a full trial, ensuring that resources allocated to fully powered trials are testing mechanisms that have strong preliminary evidence.

Step 4: Confirm target engagement: Once initial evidence is established for a relationship between the implementation strategy and the selected target, additional pilot testing is warranted. Pilot data should be collected to confirm that the relationship between the strategy and the target is robust and consistent. Then, in a fully powered sample, the next step is to confirm that the implementation strategy exerts a specific, dose-contingent effect on the target, which in turn drives a change in the outcome. This is where typical mechanism testing begins. In experimental therapeutics testing, the preceding steps are conducted to ensure that the fully powered trial is examining a mechanism that has strong evidence for being engaged by the selected implementation strategy and ensuring that any null findings could not be explained by inadequate "dosing." This approach facilitates definitive mechanism testing (i.e., the ability to conclude that a putative mechanism does not warrant additional testing), which enhances knowledge gained even if the implementation strategy is not found to be effective.

Notably, the steps outlined by Lewis and colleagues (2018) for building causal pathways are parallel to the process of conducting precision testing within an implementation science framework. Lewis and colleagues (2018) outline the following steps: (a) specify implementation strategies; (b) generate strategy-mechanism linkages; (c) identify proximal and distal outcomes. The first three steps that we describe above are generally consistent with Lewis and colleagues' (2018) steps. However, the addition of moderating variables, such as cognitive and organizational factors described by Lewis and colleagues (2018) as the fourth and final step (articulating effect modifiers), is likely to *optimize* implementation strategies. Using an experimental therapeutics approach, this would be initially measured in pilot studies, and assessed with fully powered analyses through follow up studies after initial precision testing to establish mechanisms.

Example Study Series

To illustrate a precision implementation approach, we describe a series of three studies as a case example. These studies focus on increasing provider delivery behaviors that improve the quality of exposure therapy, an evidence-based intervention for anxiety and obsessive-compulsive disorder (OCD) that involves having patients gradually approach feared situations. The first study took place in the context of efficacy studies to inform research in the second and third studies, which took place in routine clinical care settings. All three studies and their relationships to each step of the experimental therapeutics approach to mechanism testing are depicted visually in Fig. 2.

The first study in this case series is consistent with Step 1 of the experimental therapeutics approach. It illustrates provider behavior target identification, in which a potential mechanism is identified. Specifically, potential targets were assessed by examining the in-session behavior of clinical trial therapists who provided Cognitive Behavioral Therapy (CBT) in three large randomized clinical efficacy studies for pediatric OCD (Pediatric OCD Treatment Study trials;

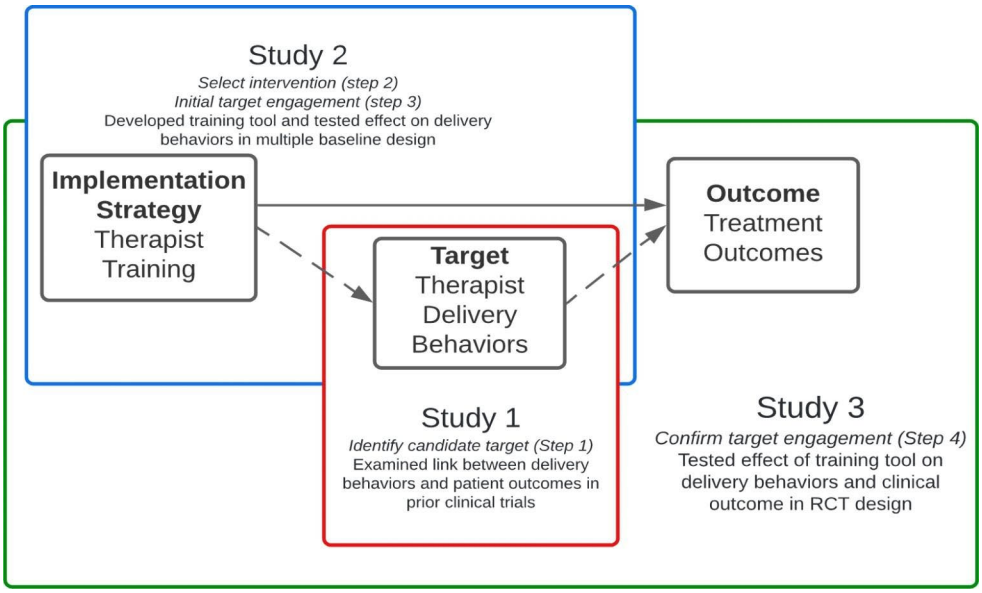

Fig. 2 Study series mapped onto experimental therapeutics mechanism testing framework

POTS team, 2004; Franklin et al., 2011; Freeman et al., 2014). Benito and colleagues (2018) developed an observational coding system to code provider behaviors; these behaviors were defined according to theorized function on patient anxiety level during exposure tasks (i.e., increase, decrease, or maintain anxiety). Function is highly relevant for the presumed mechanisms of behavioral components in CBT and theory suggests that it should have a causal link to patient outcomes. Results demonstrated that provider behaviors functioning to increase or maintain anxiety predict improved outcomes, while anxiety-decreasing behaviors predict attenuated outcomes (Benito et al., 2018) . These results support provider behavior as a promising implementation target through which CBT quality and patient outcomes could be improved.

The second study incorporates Step 2: intervention development and Step 3: demonstrate target engagement. Using observational coding results from the first study and an iterative process with community partners, authors developed a novel training tool for providers (the Exposure Guide; EG). The EG is a principle-based and user-friendly training tool that can be completed in under 5 minutes and was designed to help providers understand the function of their own behavior during exposure delivery. A small multiple baseline trial was used to assess whether addition of the EG impacts provider behaviors over and above a standard principle-based training approach. Providers ($N=6$) first received training and supervision in exposure therapy for children with OCD without the EG (baseline phase) and then received training and supervision with the EG (active phase). Results show that community providers met clinical trial benchmarks for in-session target behaviors only *after* the EG was added to standard training—providing initial evidence of target engagement (Benito et al., 2021a) . Although this study was not designed to evaluate the effects of training phase on patient clinical outcomes, results preliminarily suggest improvement rates similar to those in clinical trials.

The final study describes the process of Step 4: confirming target engagement, in a cluster randomized controlled trial . Providers ($N=16$) were recruited across two practice settings (community mental health and private practice) to deliver exposure therapy to youth with anxiety and/or OCD ($N=48$). All providers received initial workshop training and standard consultation with a flexible treatment manual; half were randomly assigned to have EG training embedded into workshop and consultation. Results show that the targeted provider behaviors (i.e., more anxiety-increasing behaviors and fewer anxiety-decreasing behaviors) were significantly improved in the EG condition. Furthermore, results provide an initial signal of higher treatment response rate among patients treated by EG-trained therapists (Benito et al., 2021b) . Importantly, this study also examined a moderating contextual factor (community mental health or private practice setting) and collected additional data related to contextual determinants at multiple levels (organizational, provider, and patient-level factors) that may be used for exploratory analysis and to guide the design of future trials. Together, these studies illustrate the process of using a mechanism-informed approach to identifying and intervening on targeted provider behaviors to optimize treatment outcome in routine clinical settings.

Table 1 Examples of precision implementation research conducted at different ecological levels

Ecological Level	Step 1: Identify target	Step 2: Select/ Design Intervention	Step 3: Demonstrate Target Engagement	Step 4: Confirm Target Engagement
Provider	Therapist delivery behaviors	Therapist training	Test effect of training tool on delivery behaviors	Test effect of training tool on delivery behavior and clinical outcome
Organization	Implementation Leadership	Coaching calls	Assess effect of coaching calls on implementation leadership	Test effect of coaching calls on implementation leadership and fidelity
Patient/ Consumer	Patient knowledge	Key opinion leaders	Test whether involving key opinion leaders in disseminating information improves patient knowledge	Test effect of partnering with key opinion leaders to disseminate information on patient knowledge and treatment seeking behavior
Policy	Policymaker attitudes toward research	Tailored policy briefs	Examine whether developing tailored policy briefs changes policymakers' attitudes toward research	Test effect of tailored policy briefs on policymakers' attitudes and subsequent policy actions

Limitations

Although there are many strengths to the approach described in this study series, there remain some limitations. First, a precision implementation approach requires initially focusing on mechanisms of individual implementation strategies, which may be time intensive. However, it is important to note that this does not mean that implementation strategies need to be tested separately before they can be combined. Instead, it suggests that a carefully designed measurement plan is needed to capture relevant targets for *each* implementation strategy. As this body of research develops, a repository of mechanisms that includes contributions from many investigators will allow for more rapid advancement of mechanism testing across multiple contexts. Despite the initial time investment, conducting precision implementation pilot tests of target engagement is ultimately a more efficient way to ensure that larger expenditures of time and money are reserved for testing strategies with established evidence for their mechanisms. Importantly, this will require coordinated efforts across many investigators and trials to advance the evidence base for understanding implementation mechanisms. To support this, it is critical to publish results from "failed" trials and to follow standardized reporting guidelines (e.g., Proctor et al., 2013; Rudd et al., 2020). Furthermore, when selecting implementation strategies, targets, and potential mechanisms, it is advisable to draw on the wealth of behavior change theory and existing literature that may help predict functional relationships and/or optimal ordering among individual strategies. This is analogous to psychosocial treatment manuals that place psychoeducation at the beginning of treatment with the reasoning that increased knowledge (via psychoeducation) is needed to inform engagement in other treatment components. The ordering of treatment components or implementation strategies should be theoretically informed but may not be empirically tested in early research. Over time, understanding individual mechanisms will inform research that examines more complexity, such as whether multiple strategies are more effective at engaging a single mechanism and whether the delivery or ordering of strategies affects mechanism engagement.

A second limitation of the case series is that it is focused on provider-level factors, which is only one of many relevant levels for implementation strategies to target. To supplement this case series and illustrate the application of the precision implementation approach to other contexts, we provide additional examples of implementation mechanisms that might be tested at different ecological levels in Table 1. In the following section, we provide additional considerations for advancing experimental therapeutics along the translational spectrum.

Applying Experimental Therapeutics to Implementation Science: Key Considerations

Complexity in Settings Where Implementation Research Takes Place

One notable challenge to the use of a precision implementation approach to mechanism testing is that it does not fully account for the complexity of the settings in which implementation research takes place. Implementation theories, models, and frameworks identify multiple system levels that are relevant to implementation (Nilsen, 2015). As noted by Williams (2016), there are likely to be relevant mechanisms at each level that interact with one another. In addition, contextual determinants (Kemp et al., 2019) operate

across multiple levels and can function as preconditions (i.e., mechanism will not be activated in their absence), moderators (i.e., interact with mechanisms to strengthen or weaken influence on outcomes), or mechanisms themselves (i.e., an implementation strategy may change a contextual variable, which will in turn change implementation outcomes). The precision implementation approach of initially assessing mechanisms linearly (i.e., strategy-mechanism-outcome) does not allow for simultaneous assessment of multiple interacting mechanisms with a traditional randomized controlled design. However, alternative study designs, such as the use of SMART designs (Almirall et al., 2014) or multiple baseline series may allow for manipulation and assessment of more than one strategy per trial. There are also several complementary and alternative methods to assessing and testing implementation mechanisms, such as the use of qualitative inquiry (e.g., Connell et al., 2016) and emerging mathematical methods (e.g., Coincidence Analysis; Whitaker et al., 2020). A research agenda detailing additional approaches and priorities for implementation mechanism testing is forthcoming (For protocol, see Lewis et al., 2021).

Over time, the precision approach to mechanism testing will produce knowledge of specific mechanisms that can be easily understood by a variety of stakeholders and that can apply to a wide array of contexts. Furthermore, repeated precision testing in different contexts and at different time points will allow for aspects of context to vary. If manipulating a mechanism produces robust effects across multiple contexts, this provides strong evidence that the mechanism is likely to generalize. Once the relationship between an implementation strategy, a mechanism (or target), and an implementation outcome is established, this will allow for a better understanding of the influence of contextual factors. It will also allow for more efficient testing of multi-level mechanisms using the statistical approaches described by Williams (2016).

The Role of Pilot Studies

A major limitation of existing implementation research is that little is known about the active ingredients of implementation strategies. One study showed that a median of 33 implementation strategies were used in implementation studies (Rogal et al., 2017), but only some were associated with treatment outcomes. This suggests that resources are likely being wasted on employing several implementation strategies that do not influence outcomes and that may include inert ingredients. Although precision implementation testing may be resource intensive in the short term, it is likely to save resources in the long term given its contributions to improving appropriate selection of implementation strategies. Specifically, precision implementation places an emphasis on quick, methodologically sound pilots that are designed to "fail fast" when target engagement is not established. Thus, although a pilot study will not meet all seven of Kazdin's (2007) criteria for establishing mechanisms, it will provide necessary information to allow a fully powered trial to meet most, if not all, of these criteria.

Pilot studies for implementation research typically focus on outcomes such as feasibility and acceptability. In addition to assessing these key outcomes, pilot studies offer an opportunity to assess target engagement by examining the strength of an implementation strategy's effect on the target. Notably, precision implementation studies may test more than one implementation strategy at a time but doing so requires careful consideration of the timing of implementation strategy delivery and measurement of the hypothesized target. At the same time, other factors (e.g., pre-conditions, moderators) can naturally vary. Having a thorough measurement plan will allow for precise assessment of mechanisms, while also gaining an understanding of how particular settings and moderating factors may influence a strategy's effect.

Target selection is also a critical aspect of designing an appropriate pilot study. There are two particularly important considerations for selecting appropriate targets: (1) the potential effect size of the implementation strategy on the target and (2) the potential for the target to lead to a change in a meaningful outcome. Given that targets are a more proximal outcome than implementation outcomes, there is likely to be a stronger effect of the implementation strategy on the target than on the more distal outcome of interest. For instance, an organizational intervention (*the implementation strategy*) that has a small effect on implementation leadership *(the target*) in a pilot trial is unlikely to lead to meaningful change in adoption of an intervention *(implementation outcome*). However, if the implementation strategy has a large effect on the *target* (implementation leadership), this would indicate promise to proceed with this strategy in a larger trial. Thus, pilot trials can be used to assess whether the implementation strategy exerts a large and/or meaningful change to the target as demonstrated by *a priori* effect sizes or benchmarks. Of note, this does *not* suggest that there should be an attempt to estimate an effect size for the larger trial based on the pilot data (Sim, 2019). Instead, pilot studies should be used to assess target engagement, as measured by benchmarks or effect sizes for the *target*.

For more complex implementation strategies, it might also be appropriate to assess their component parts. For instance, strategies such as the leadership and organizational change for implementation (LOCI; Aarons et al., 2015) include multiple components: (1) assessment, (2) didactic training with leadership development planning; (3) coaching; (4)

organizational strategy development; (5) booster session; (6) graduation. Using a precision implementation approach, a pilot study might assess target engagement for each of these components. Although this could involve delivering each component separately, this package of implementation strategies could also be implemented together as long as mechanisms are measured appropriately for each strategy with careful attention to timing. Hypothesized targets should be measured close in time to delivery of the corresponding implementation strategy. For instance, LOCI components may target leadership knowledge (via didactic training), motivation (via coaching), and implementation climate (via organizational strategy development). If these implementation strategies (LOCI components) are best delivered as a package for maximum effect, researchers might measure each of the targets (e.g., knowledge, motivation, implementation climate) throughout implementation using an assessment schedule that logically matches the timeframe during which change would be expected to occur. If change in targets is seen in conjunction with the corresponding components (but not with other components), this would provide strong initial evidence of target engagement.

Another approach for pilot studies is the use of small *N* designs, such as multiple baseline studies, especially if changes to the target can be compared to a meaningful benchmark based on prior studies. Using the example of an organizational intervention, benchmark scores on the Implementation Leadership Scale (ILS; Aarons et al., 2014) could be used to assess what "dose" of the organizational intervention is needed for implementation leadership levels to reach these benchmarks. Such benchmarks should ideally be linked to the outcome of interest. For instance, if the outcome of interest is fidelity to the intervention, benchmark scores should be selected by identifying ILS scores that were associated with high fidelity in prior research. Benchmark scores and other guidelines, such as what percentage of people need to meet the benchmark and in what timeframe, should be decided a priori.

Need for Repeated Measurement

One difficulty with establishing mechanisms is the need for rigorous and repeated measurement, which may be particularly challenging given that implementation science already has a dearth of appropriate measures. However, experimental therapeutics often considers targets that may have existing and relevant measures from other disciplines. For example, the measurement of intentions has been studied in many mechanistic studies conducted in social psychology research, and many of these validated measures have recently been applied to implementation science (Fishman et al., 2020). Rigorous measurement is essential for isolating and distinguishing a change mechanism. This begins by establishing operational definitions of the mechanism(s) and outcome(s) of interest and using measures that are appropriately reliable and sensitive to change. The basic framework for mechanism testing mentioned above is necessary for establishing mechanism effects, but the test can be strengthened to the extent that temporality and degree of change in the mechanism is shown to influence outcomes (Nock, 2007). To reduce the burden of repeatedly administering measures throughout an intervention, researchers should determine the place and time when change is most likely to occur and start by focusing measurement around these candidate events. For example, a target such as knowledge is most likely to change immediately following an implementation strategy involving training, so knowledge should be assessed as close as possible in time to any dose of training. Ideally, measurement of mechanisms should occur repeatedly, detect gradients of change, and include alternative plausible mechanisms to demonstrate the specificity of the change mechanism of interest.

Levels of Analysis

A key aspect of the precision implementation approach to assessing mechanisms is to identify a level of analysis and ensure that the implementation strategy, mechanism, and outcome are all on the same level. This approach to mechanism testing is consistent across the translational spectrum, but the *selection* of mechanisms depends on the level of analysis. In other words, what constitutes a relevant mechanism may differ depending on the granularity of an intervention's primary independent variable (e.g., neurochemical levels, treatment history, organization resources) and dependent variable (e.g., circuitry function, treatment response, practitioner behavior). Given the multi-level influences on implementation outcomes (Lewis et al., 2018; Williams, 2016), it is especially important to ensure that mechanism testing takes place at consistent levels. For instance, an implementation strategy focused on changing provider behavior (e.g., training) should aim to engage a provider-level mechanism (e.g., knowledge) and lead to a change in a provider-level outcome (e.g., individual prescribing behavior). If an implementation strategy is focused on an organization-level construct (e.g., facilitating team meetings), the mechanism (e.g., organizational norms) and outcomes (e.g., organization's adoption of an intervention) should also occur at this level. As research on implementation mechanisms advances, there are likely to be more examples of precision implementation studies that simultaneously examine multi-level mechanisms, such as using facilitation as an implementation strategy at the organizational level and examining provider- and organization-level mechanisms

(e.g., reducing burnout for providers; decreasing turnover at the organization level). Hybrid designs (Curran et al., 2012; Kemp et al., 2019) may be particularly well-suited to examining multi-level mechanisms and their impact on various outcomes. However, such research will require much larger sample sizes and more complex designs to isolate the effects of individual mechanisms.

Mechanism selection should be guided by a strong empirical rationale that logically links intervention, mechanism, and outcome. Implementation outcomes are important at each level of change, but the research has yet to determine which level or unit of analysis is most appropriate for particular implementation outcomes. Certain outcomes, such as acceptability, may be most appropriate for individual-level analysis (e.g., providers, consumers), while others such as penetration may be more appropriate for aggregate analysis (e.g., at the level of the health care organization). This is consistent with Williams (2016), who calls for the alignment of level of analysis with level of theory.

Conclusion

The precision implementation approach for testing mechanisms is consistent with the NIMH's call for using experimental therapeutics, as well as the NIH-supported Science of Behavior Change. This paper highlights how funders' requests for mechanism-focused research can be applied to implementation science. The precision implementation approach has many strengths, including its ability to serve as foundational research for more complex assessment of mechanisms in "real world" clinical settings. In addition, it addresses existing limitations to mechanistic research by using rigorous methods that are likely to meet all criteria for establishing a mechanism (Kazdin, 2007) if the entire study series, include a fully powered trial, is completed. The precision implementation approach is particularly well suited to examine dose-response relationships between mediators and outcomes, which has rarely been assessed in implementation studies (Lewis et al., 2020). There is a need for additional "proof of concept" research studies that establish the application of the experimental therapeutics approach in implementation science. These studies can also confirm that mechanisms function similarly for different contexts and research studies. This research can then be used to build the evidence base for mechanisms underlying implementation strategies and the "core components" of implementation strategies, which can be combined and moderated by contextual factors.

Authors' Contributions HF and JK conceived of the idea for this manuscript and collaboratively generated an outline, drafted the manuscript, and substantially revised it. KB provided input at every stage of the manuscript and led the studies that are discussed in the case example. JF helped conceive of the manuscript idea and was a multiple PI on the studies described in the case example. All authors read and approved the final manuscript.

Funding Funding was provided from the National Institute of Mental Health to Dr. Frank (T32) and Dr. Kemp (R34). The funding body did not have any direct role in the manuscript idea or writing of the manuscript.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflicts of Interest The authors declare that they have no competing interests.

Ethics Approval and Consent Not applicable.

Research involving Human Participants and/or Animals Not applicable.

Informed Consent Not applicable.

References

Aarons, G. A., Ehrhart, M. G., & Farahnak, L. R. (2014). The Implementation Leadership Scale (ILS): development of a brief measure of unit level implementation leadership. *Implement Sci*, *9*(1), 45. doi:https://doi.org/10.1186/1748-5908-9-45

Aarons, G. A., Ehrhart, M. G., Farahnak, L. R., & Hurlburt, M. S. (2015). Leadership and organizational change for implementation (LOCI): a randomized mixed method pilot study of a leadership and organization development intervention for evidence-based practice implementation. *Implementation Science*, *10*(1), 11. doi:https://doi.org/10.1186/s13012-014-0192-y

Alexander, J. A., & Hearld, L. R. (2012). Methods and metrics challenges of delivery-system research. *Implementation Science*, *7*(1), 15. doi:https://doi.org/10.1186/1748-5908-7-15

Almirall, D., Nahum-Shani, I., Sherwood, N. E., & Murphy, S. A. (2014). Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. *Translational Behavioral Medicine*, *4*(3), 260–274. doi:https://doi.org/10.1007/s13142-014-0265-0

Benito, K. G., Machan, J., Freeman, J. B., Garcia, A. M., Walther, M., Frank, H., & Franklin, M. (2018). Measuring fear change within exposures: Functionally-defined habituation predicts outcome in three randomized controlled trials for pediatric OCD. *Journal Of Consulting And Clinical Psychology*, *86*(7), 615–630. doi:https://doi.org/10.1037/ccp0000315

Chambers, D. A., Feero, W. G., & Khoury, M. J. (2016). Convergence of implementation science, precision medicine, and the learning health care system: a new model for biomedical research. *Journal Of The American Medical Association*, *315*(18), 1941–1942

Chanfreau-Coffinier, C., Peredo, J., Russell, M. M., Yano, E. M., Hamilton, A. B., Lerner, B., & Scheuner, M. T. (2019). A logic model for precision medicine implementation informed by stakeholder views and implementation science. *Genetics in Medicine*, *21*(5), 1139–1154

Pediatric OCD Treatment Study (POTS) Team (2004). Cognitive-behavior therapy, sertraline, and their combination for children

and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA, 292*(16), 1969–1976. https://doi.org/10.1001/jama.292.16.1969

Colquhoun, H. L., Brehaut, J. C., Sales, A., Ivers, N., Grimshaw, J., Michie, S., & Eva, K. W. (2013). A systematic review of the use of theory in randomized controlled trials of audit and feedback. *Implementation Science*, *8*(1), 66. doi:https://doi.org/10.1186/1748-5908-8-66

Connell, L. A., McMahon, N. E., Tyson, S. F., Watkins, C. L., & Eng, J. J. (2016). Mechanisms of action of an implementation intervention in stroke rehabilitation: a qualitative interview study. *BMC Health Services Research*, *16*(1), 534. doi:https://doi.org/10.1186/s12913-016-1793-8

Curran, G. M., Bauer, M., Mittman, B., Pyne, J. M., & Stetler, C. (2012). Effectiveness-implementation Hybrid Designs. *Medical Care*, *50*(3), 217–226. doi:https://doi.org/10.1097/mlr.0b013e3182408812

Fishman, J., Lushin, V., & Mandell, D. S. (2020). Predicting implementation: comparing validated measures of intention and assessing the role of motivation when designing behavioral interventions. *Implementation Science Communications*, *1*(1), doi:https://doi.org/10.1186/s43058-020-00050-4

Franklin, M. E., Sapyta, J., Freeman, J. B., Khanna, M., Compton, S., Almirall, D., & March, J. S. (2011). Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder: The Pediatric OCD Treatment Study II (POTS II) randomized controlled trial. *JAMA: Journal of the American Medical Association*, *306*(11), 1224–1232. doi:https://doi.org/10.1001/jama.2011.1344

Freeman, J., Sapyta, J., Garcia, A., Compton, S., Khanna, M., Flessner, C., & Franklin, M. (2014). Family-Based Treatment of Early Childhood Obsessive-Compulsive Disorder: The Pediatric Obsessive-Compulsive Disorder Treatment Study for Young Children (POTS Jr)-A Randomized Clinical Trial. *JAMA Psychiatry*. doi:https://doi.org/10.1001/jamapsychiatry.2014.170

French, S. D., Green, S. E., O'Connor, D. A., McKenzie, J. E., Francis, J. J., Michie, S., & Grimshaw, J. M. (2012). Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. *Implement Sci*, *7*, 38. doi:https://doi.org/10.1186/1748-5908-7-38

Geng, E. H., Baumann, A. A., & Powell, B. J. (2022). Mechanism mapping to advance research on implementation strategies. *Plos Medicine*, *19*(2), e1003918. doi:https://doi.org/10.1371/journal.pmed.1003918

Grabb, M. C., Hillefors, M., & Potter, W. Z. (2020). The NIMH 'Fast-Fail Trials' (FAST) Initiative: Rationale, Promise, and Progress. *Pharmaceutical Medicine*, *34*(4), 233–245. doi:https://doi.org/10.1007/s40290-020-00343-y

Insel, T. R. (2015). The NIMH experimental medicine initiative. *World Psychiatry*, *14*(2), 151–153. doi:https://doi.org/10.1002/wps.20227

Insel, T. R., & Gogtay, N. (2014). National Institute of Mental Health clinical trials: new opportunities, new expectations. *JAMA Psychiatry*, *71*(7), 745–746. doi:https://doi.org/10.1001/jamapsychiatry.2014.426

Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annual Review of Clinical Psychology*, *3*, 1–27. doi:https://doi.org/10.1146/annurev.clinpsy.3.022806.091432

Kemp, C. G., Wagenaar, B. H., & Haroz, E. E. (2019). Expanding Hybrid Studies for Implementation Research: Intervention, Implementation Strategy, and Context. *Frontiers in Public Health*, *7*, doi:https://doi.org/10.3389/fpubh.2019.00325

Lewandowski, K. E., Ongur, D., & Keshavan, M. S. (2018). Development of novel behavioral interventions in an experimental therapeutics world: Challenges, and directions for the future. *Schizophrenia Research*, *192*, 6–8. doi:https://doi.org/10.1016/j.schres.2017.06.010

Lewis, C. C., Boyd, M. R., Walsh-Bailey, C., Lyon, A. R., Beidas, R., Mittman, B., & Chambers, D. A. (2020). A systematic review of empirical studies examining mechanisms of implementation in health. *Implement Sci*, *15*(1), 21. doi:https://doi.org/10.1186/s13012-020-00983-3

Lewis, C. C., Klasnja, P., Powell, B. J., Lyon, A. R., Tuzzio, L., Jones, S., & Weiner, B. (2018). From Classification to Causality: Advancing Understanding of Mechanisms of Change in Implementation Science. *Frontiers in Public Health*, *6*, doi:https://doi.org/10.3389/fpubh.2018.00136

Lewis, C. C., Powell, B. J., Brewer, S. K., Nguyen, A. M., Schriger, S. H., Vejnoska, S. F., & Mittman, B. (2021). Advancing mechanisms of implementation to accelerate sustainable evidence-based practice integration: protocol for generating a research agenda. *BMJ open*, *11*(10), e053474. doi:https://doi.org/10.1136/bmjopen-2021-053474

Lyon, A. R., Dopp, A. R., Brewer, S. K., Kientz, J. A., & Munson, S. A. (2020). Designing the Future of Children's Mental Health Services. *Administration and Policy in Mental Health and Mental Health Services Research*, *47*(5), 735–751. doi:https://doi.org/10.1007/s10488-020-01038-x

Lyon, A. R., & Koerner, K. (2016). User-centered design for psychosocial intervention development and implementation. *Clinical Psychology: Science and Practice*, *23*(2), 180–200. doi:https://doi.org/10.1111/cpsp.12154

Mettert, K., Lewis, C., Dorsey, C., Halko, H., & Weiner, B. (2020). Measuring implementation outcomes: An updated systematic review of measures' psychometric properties. *Implementation Research and Practice*, *1*, 263348952093664. doi:https://doi.org/10.1177/2633489520936644

Michie, S., Fixsen, D., Grimshaw, J. M., & Eccles, M. P. (2009). Specifying and reporting complex behaviour change interventions: the need for a scientific method. *Implementation Science*, *4*(1), 40. doi:https://doi.org/10.1186/1748-5908-4-40

Nielsen, L., Riddle, M., King, J. W., Aklin, W. M., Chen, W., Clark, D., & Weber, W. (2018). The NIH Science of Behavior Change Program: Transforming the science through a focus on mechanisms of change. *Behaviour Research And Therapy*, *101*, 3–11. doi:https://doi.org/10.1016/j.brat.2017.07.002

Nilsen, P. (2015). Making sense of implementation theories, models and frameworks. *Implementation Science*, *10*(1), doi:https://doi.org/10.1186/s13012-015-0242-0

Nock, M. K. (2007). Conceptual and Design Essentials for Evaluating Mechanisms of Change. *Alcoholism: Clinical and Experimental Research, 31*(s3), 4s-12s. doi:https://doi.org/10.1111/j.1530-0277.2007.00488.x

Powell, B. J., Beidas, R. S., Lewis, C. C., Aarons, G. A., McMillen, J. C., Proctor, E. K., & Mandell, D. S. (2017). Methods to Improve the Selection and Tailoring of Implementation Strategies. *The Journal of Behavioral Health Services & Research*, *44*(2), 177–194. doi:https://doi.org/10.1007/s11414-015-9475-6

Powell, B. J., Fernandez, M. E., Williams, N. J., Aarons, G. A., Beidas, R. S., Lewis, C. C., & Weiner, B. J. (2019). Enhancing the Impact of Implementation Strategies in Healthcare: A Research Agenda. *Frontiers in Public Health*, *7*, doi:https://doi.org/10.3389/fpubh.2019.00003

Powell, B. J., Mettert, K. D., Dorsey, C. N., Weiner, B. J., Stanick, C. F., Lengnick-Hall, R., & Lewis, C. C. (2021). Measures of organizational culture, organizational climate, and implementation climate in behavioral health: A systematic review. *Implementation Research and Practice*, *2*, 263348952110188. doi:https://doi.org/10.1177/26334895211018862

Powell, B. J., Waltz, T. J., Chinman, M. J., Damschroder, L. J., Smith, J. L., Matthieu, M. M., & Kirchner, J. E. (2015). A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implementation Science*, *10*(1), 21. doi:https://doi.org/10.1186/s13012-015-0209-1

Proctor, E. K., Powell, B. J., & McMillen, J. C. (2013). Implementation strategies: recommendations for specifying and reporting. *Implementation Science*, *8*(1), 139. doi:https://doi.org/10.1186/1748-5908-8-139

Proctor, E. K., Silmere, H., Raghavan, R., Hovmand, P., Aarons, G., Bunger, A., & Hensley, M. (2011). Outcomes for Implementation Research: Conceptual Distinctions, Measurement Challenges, and Research Agenda. *Administration and Policy in Mental Health and Mental Health Services Research*, *38*(2), 65–76. doi:https://doi.org/10.1007/s10488-010-0319-7

Raghavan, R., Munson, M. R., & Le, C. (2019). Toward an Experimental Therapeutics Approach in Human Services Research. *Psychiatric Services (Washington, D. C.)*, *70*(12), 1130–1137. doi:https://doi.org/10.1176/appi.ps.201800577

Rogal, S. S., Yakovchenko, V., Waltz, T. J., Powell, B. J., Kirchner, J. E., Proctor, E. K., & Chinman, M. J. (2017). The association between implementation strategy use and the uptake of hepatitis C treatment in a national sample. *Implementation Science*, *12*(1), doi:https://doi.org/10.1186/s13012-017-0588-6

Rudd, B. N., Davis, M., & Beidas, R. S. (2020). Integrating implementation science in clinical research to maximize public health impact: a call for the reporting and alignment of implementation strategy use with implementation outcomes in clinical research. *Implementation Science*, *15*(1), doi:https://doi.org/10.1186/s13012-020-01060-5

Sim, J. (2019). Should treatment effects be estimated in pilot and feasibility studies? *Pilot and Feasibility Studies*, *5*(1), 107. doi:https://doi.org/10.1186/s40814-019-0493-7

Whitaker, R. G., Sperber, N., Baumgartner, M., Thiem, A., Cragun, D., Damschroder, L., & Birken, S. (2020). Coincidence analysis: a new method for causal inference in implementation science. *Implementation Science*, *15*(1), 108. doi:https://doi.org/10.1186/s13012-020-01070-3

Williams, N. J. (2016). Multilevel Mechanisms of Implementation Strategies in Mental Health: Integrating Theory, Research, and Practice. *Administration and Policy in Mental Health and Mental Health Services Research*, *43*(5), 783–798. doi:https://doi.org/10.1007/s10488-015-0693-2

Benito, K. G., Herren, J., Freeman, J. B., Garcia, A. M., Block, P., Cantor, E., Chorpita, B. F., Wellen, B., Stewart, E., Georgiadis, C., Frank, H., & Machan, J. (2021a). Improving Delivery Behaviors During Exposure for Pediatric OCD: A Multiple Baseline Training Trial With Community Therapists. Behavior therapy, 52(4), 806–820. https://doi.org/10.1016/j.beth.2020.10.003

Benito, K. G., Herren, J., Freeman, J. B., Garcia, A. M., Kemp, J., Chorpita, B. F., Sung, J., Arora, A., Georgiadis, C., Stewart, E., Wellen, B., Frank, H. E., Schiavone, E., Gervasio, M., & Machan, J. (2021b). Improving Delivery Behaviors During Exposure Therapy: A Cluster Randomized Controlled Training Trial with Community Therapists. Evidence-Based Practice in Child and Adolescent Mental Health, 6(2), 173-190. https://doi.org/10.1080/23794925.2021.1917018

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com