Applying Translational Science Approaches to Protect Workers Exposed to Nanomaterials

Paul A. Schulte 1*, Rebecca J. Guerin 2, Thomas R. Cunningham 2, Laura Hodson 2, Vladimir Murashov 3 and Borsika Adrienn Rabin 4

1 Advanced Technologies and Laboratories (ATL) International, Inc., Gaithersburg, MD, United States, 2 National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, United States, 3 National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Washington, DC, United States, 4 University of California, San Diego, San Diego, CA, United States

Like nanotechnology, translational science is a relatively new and transdisciplinary field. Translational science in occupational safety and health (OSH) focuses on the process of taking scientific knowledge for the protection of workers from the lab to the field (i.e., the worksite/workplace) and back again. Translational science has been conceptualized as having multiple phases of research along a continuum, beyond scientific discovery (T0), to efficacy (T1), to effectiveness (T2), to dissemination and implementation (D&I) (T3), to outcomes and effectiveness research in populations (T4).

The translational research process applied to occupational exposure to nanomaterials might involve similar phases. This builds on basic and efficacy research (T0 and T1) in the areas of toxicology, epidemiology, industrial hygiene, medicine and engineering. In T2, research and evidence syntheses and guidance and recommendations to protect workers may be developed and assessed for effectiveness. In T3, emphasis is needed on D&I research to explore the multilevel barriers and facilitators to nanotechnology risk control information/research adoption, use, and sustainment in workplaces. D&I research for nanomaterial exposures should focus on assessing sources of information and evidence to be disseminated/implemented in complex and dynamic workplaces, how policy-makers and employers use this information in diverse contexts to protect workers, how stakeholders inform these critical processes, and what barriers impede and facilitate multilevel decision-making for the protection of nanotechnology workers. The T4 phase focuses on how effective efforts to prevent occupational exposure to nanomaterials along the research continuum contribute to large-scale impact in terms of worker safety, health and wellbeing (T4). Stakeholder input and engagement is critical to all stages of the translational research process. This paper will provide: (1) an illustration of the translational research continuum for occupational exposure to nanomaterials; and (2) a discussion of opportunities for applying D&I science to increase the effectiveness, uptake, integration, sustainability, and impact of interventions to protect the health and wellbeing of workers in the nanotechnology field.

Keywords: dissemination, implementation, nanotechnology, research, impact
INTRODUCTION

Nanotechnology and the development of nanomaterials have yielded a large number of commercial products and exposures to workers (1–3). The diffusion of nanotechnology into commerce in the early 2000's raised concern about potential hazards to workers (4–6). The small particle size, novel characteristics of nanoparticles and hypotheses about interaction with biological molecules and structures prompted public health authorities to consider whether workers could be at risk of adverse effects from exposure to engineered nanomaterials (ENM). To prevent such effects, if they were to occur, occupational public health authorities promoted and conducted research and issued guidance for employers and workers on risk management (6–8). The overarching questions are identifying the extent to which guidance was used, and whether the guidance made a difference in the health and safety of workers. Unfortunately, these and related questions have not been the focus of much research. In fact, such research has rarely, with notable exceptions, been considered or implemented in the occupational health field, in general, let alone in the area of exposure of workers to ENM (9–11). To address this shortfall there has been an effort in recent years to promote research on the “downstream” part of a continuum beyond basic research to impact (Figure 1) (11). This research, which includes dissemination and implementation (D&I) research, can fall under the umbrella of “translational science.” Traditionally, translational science has focused largely on barriers to intervention development at the efficacy and effectiveness stages (T₁ and T₂). Once an evidence base is established, D&I science has focused on barriers to the adoption, use, and sustainment (T₃ and T₄) of evidence-based interventions (12). Table 1 illustrates key characteristics of dissemination and implementation research and hypothetical examples for the occupational safety and health field. Figure 1 depicts the translational science cycle, conceptualized as crossing all translational or “T” phases of the research continuum, from scientific discovery (T₀) to efficacy (T₁), effectiveness (T₂), dissemination and implementation (T₃), and the outcomes and effectiveness and impact of research in populations (T₄).

OSH interventions (such as those represented in Table 2) may be situated anywhere along the research continuum, and, in reality, do not necessarily pass through all the T stages. In the context of OSH research (and beyond), there is a dearth of research conducted in the T₃ and T₄ stages of the research continuum (14).

While closely connected, the primary focus of translational science is not to do translation or its synonymous activity, research-to-practice (R2P) [an approach to collaborations with partners on the adoption, use, and adaptation of knowledge, interventions and technologies (15)]. Rather, it is the study of

---

**Figure 1** | Overview of translational science for occupational safety and health [adapted from Schulte et al. (11)].
how these activities and processes (i.e., uptake, implementation, sustained use) work, what their multilevel barriers and facilitators are, and what intermediate and ultimate impacts they have on diverse outcomes. It should be noted that the processes shown in Figure 1 are not linear but represent a dynamic and iterative interplay across stages and involve many factors that interact and provide feedback to previous and consecutive stages. The challenge is to study the main causal factors while accounting for and acknowledging the complex context within which they exist.

Ultimately, there is a need to investigate many casual pathways that influence worker safety and health outcomes. Sorensen et al. (16) developed a conceptual model “based on the premise that addressing multiple pathways in an integrated manner with a focus on the conditions of work will contribute to greater impairment in worker and enterprise outcomes than addressing each pathway separately” (16). This integrated approach can guide research and intervention designs and may be a framework for T₁ and T₂ efforts.

In this paper we examine how research and guidance on ENMs are situated within the translational science continuum, and identify gaps related to, and opportunities for, increasing research efforts particularly at the later stages (T₃ and T₄) of that continuum. To that end, the paper will provide: (1) an illustration of the translational research continuum for occupational exposure to ENMs; and (2) a discussion of opportunities for expanding efforts in D&I science to increase the effectiveness, integration and impact of interventions to protect the health and wellbeing of workers in the nanotechnology field.

For illustrative purposes, we present three examples of OSH interventions— broadly defined as programs, practices, policies, recommendations, and guidelines (17)—that can be considered relevant for occupational exposure to ENMs and could give rise to translational research questions: (1) National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits for titanium dioxide (TiO₂) and carbon nanotubes and nanofibers, (CNTs/CNFs) (18, 19); (2) World Health Organization (WHO) guidelines for protecting workers from potential risks of manufactured nanomaterials.

TABLE 2 | Examples of interventions to address worker exposure to ENMs.

| Intervention | Example |
|--------------|---------|
| Program | OECD Testing Programmers of Manufactured Nanomaterials |
| Practices | Occupational Exposure Limits |
| Principle | Consider ENM hazardous until proven otherwise |
| Procedures | Nanomaterial Exposure Assessment Technique |
| Products | Direct reading instrumentation |
| Policies | ISO/TC 229 Nanotechnologies; WHO guidance on protecting workers from potential risks of manufactured nanomaterials. |

Adapted from NIH (13).
and can be based on the synthesis of information and peer review of guidance or a critical review of the literature based on results from diverse study designs (e.g., cross-sectional, case control, or longitudinal studies). When establishing evidence for later stage translational work, traditional RCTs can become problematic. For example, the use of RCTs in occupational settings, arguably, could be seen as unethical if an intervention judged to be efficacious and safety or health-enhancing is withheld from some segment of the workforce exposed to a potential hazard (26, 27).

It is also important to identify what an intervention is with regard to ENMs. The interventions to protect workers from adverse effects may vary substantially. Generally, in translational science, interventions can be described in broad terms as one of the “7 Ps”: programs, practices, principles, procedures, products, pills and policies (28). In the ENM arena most of these, except pills, would be considered as interventions to address occupational hazards (Table 2). Table 2 was developed to help the nanotechnology community understand that “intervention” can have a wide range of meanings. These interventions can fit at all stages of Figure 1. The target audiences for translational science are the organizations and decision-makers who develop, disseminate, or implement interventions. These audiences include government authorities, decision-makers, employers, trade associations, and unions. Ultimately the interventions will be implemented to protect workers but the pathway generally will be through employers.

**TRANSLATIONAL SCIENCE**

It is useful to envision the continuum of translational science from beyond basic research through the impact of that research on populations. Translational science has been conceptualized as having multiple phases of research beyond scientific discovery (T₀), to efficacy research (T₁), to effectiveness research (T₂), to dissemination and implementation research (D&I) (T₃), to outcomes and effectiveness research in populations (T₄) (12, 29–35). From an occupational safety and health perspective, for translational research findings to make a difference in the safety and health of workers it is necessary to determine the best ways to direct basic research findings and guidance information to employers, workers and authorities promotes the uptake of that information, and determines whether it made a positive impact.

The T₀ stage is focused on scientific discovery driven by basic science. While there are important feedback loops between the T₀ and later T₁ through T₄ stages, this paper will focus on T₁ to T₄ that is, how well the products of basic research can be utilized to affect and protect ENM workers and, specifically, how to study the stages leading to such protection. To better view the stages between T₁ and T₄ this paper reviews various examples of the continuum applied to hazard information and interventions related to ENMs. In the next sections and in Tables 3–5 we present three examples.

Translational science is a field that merits support because it is a crucial that stakeholders receive and use recommendations and interventions as a means to responsible development of a technology, corporate responsibility, and worker and population wellbeing (37–42). The successful commercialization of nanotechnology depends on societal acceptance of it. Societal acceptance will be influenced by, among other things, whether workers are protected from nanotechnology hazards. When it is apparent that workers are at high risk of adverse health effects and not protected, the societal response toward

| Example 1: Recommended exposure limits (CNT/CNF & TiO₂) |
|--------------------------------------------------------|
| **T₀ Basic science**                                    | Ultratine and fiber toxicity |
| **T₁ Efficacy research**                                | Specific studies of ENMs |
| **T₂ Effectiveness research**                           | Quantitative risk assessment |
| **T₃ Dissemination & implementation research**           | Sensitivity analysis of risk assessment |
| **T₄ Population impact**                                | Historical basis for OELs |

| Example 2: WHO guidance for protecting workers |
|------------------------------------------------|
| **T₀ Basic science**                              | Historical and contemporary toxicity data |
| **T₁ Efficacy research**                           | Stakeholder requests |
| **T₂ Effectiveness research**                      | PECO analysis |
| **T₃ Dissemination & implementation research**      | International expert assessment |
| **T₄ Population impact**                           | Historical evidence |

| Example 3: International Risk Governance Council guidance |
|----------------------------------------------------------|
| **T₀ Basic science**                                    | Historic and contemporary toxicity data |
| **T₁ Efficacy research**                                | Explosiveness data |
| **T₂ Effectiveness research**                           | Stakeholder requests |
| **T₃ Dissemination & implementation research**           | Scoping review on deficit in guidance |
| **T₄ Population impact**                                | Synthesis of evidence for risk governance |

| Table 3 | Utilization of translational science pertaining to NIOSH recommended exposure limits for TiO₂ and CNT/CNF. |
|---------|-------------------------------------------------------------------------------------------------------------|
| **T₀ Basic science**                                    | Ultratine and fiber toxicity |
| **T₁ Efficacy research**                                | Specific studies of ENMs |
| **T₂ Effectiveness research**                           | Quantitative risk assessment |
| **T₃ Dissemination & implementation research**           | Sensitivity analysis of risk assessment |
| **T₄ Population impact**                                | Historical basis for OELs |

| Table 4 | WHO Guidance for protecting workers. |
|---------|--------------------------------------------------------------------------------------|
| **T₀ Basic science**                              | Historical and contemporary toxicity data |
| **T₁ Efficacy research**                           | Stakeholder requests |
| **T₂ Effectiveness research**                      | PECO analysis |
| **T₃ Dissemination & implementation research**      | International expert assessment |
| **T₄ Population impact**                           | Historical evidence |

| Table 5 | International Risk Governance Council guidance. |
|---------|------------------------------------------------------------------------------------------------------|
| **T₀ Basic science**                              | Historic and contemporary toxicity data |
| **T₁ Efficacy research**                           | Explosiveness data |
| **T₂ Effectiveness research**                      | Stakeholder requests |
| **T₃ Dissemination & implementation research**      | Scoping review on deficit in guidance |
| **T₄ Population impact**                           | Synthesis of evidence for risk governance |

| WHO (20). |
|-----------|

| Table 3 |
|---------|
| **T₀ Basic science** | Ultratine and fiber toxicity |
| **T₁ Efficacy research** | Specific studies of ENMs |
| **T₂ Effectiveness research** | Quantitative risk assessment |
| **T₃ Dissemination & implementation research** | Sensitivity analysis of risk assessment |
| **T₄ Population impact** | Historical basis for OELs |

| Table 4 | WHO Guidance for protecting workers. |
|---------|--------------------------------------------------------------------------------------|
| **T₀ Basic science** | Historical and contemporary toxicity data |
| **T₁ Efficacy research** | Stakeholder requests |
| **T₂ Effectiveness research** | PECO analysis |
| **T₃ Dissemination & implementation research** | International expert assessment |
| **T₄ Population impact** | Historical evidence |

| Table 5 | International Risk Governance Council guidance. |
|---------|------------------------------------------------------------------------------------------------------|
| **T₀ Basic science** | Historic and contemporary toxicity data |
| **T₁ Efficacy research** | Explosiveness data |
| **T₂ Effectiveness research** | Stakeholder requests |
| **T₃ Dissemination & implementation research** | Scoping review on deficit in guidance |
| **T₄ Population impact** | Synthesis of evidence for risk governance |

| IRGC (22). |
acceptance of the technology is likely to be negative (37). Therefore, it is incumbent on employers and authorities to support the development of translational science as a means to support responsible development of nanotechnology. Supporting translational science will result in broad utilization of guidance and increase involvement of stakeholders in that process (37, 43–47). For example, Brownson (47), building on work of Curry (48) and Anderson et al. (49), described a push-pull model for strategic public health science that could be adopted to strategic translational science for occupational safety and health: “This model posits that for science to effect practice there must be a combination of push (a basis in science and technology) and the pull (a market demand from practitioners), and the capacity (delivery ability of public health systems).” The adaption would be that practitioners would be considered as employers, workers, unions, trade associations, and other decision-makers that affect worker protection.

Example 1: NIOSH Recommended Exposure Limits for TiO₂ and CNT

**T₁: Basic Science - Discovery Data**

Table 3 illustrates the translational science continuum for this example. Titanium dioxide (TiO₂) and CNT/CNF are ENMs that were studied early on in the commercialization of nanotechnology [see (18, 19) for review] and found to have adverse health effects in laboratory animals. Clearly, there are many types of TiO₂ and CNT/CNF and the toxicity information only pertained to specific chemical and physical types. The type of toxicological assessments that is most relevant to occupational safety and health are rodent inhalation studies. TiO₂ and other poorly soluble particles of low toxicity (PSLT) of fine and ultrafine sizes were found to show consistent dose-response relationships for adverse pulmonary inflammation and lung tumors when dose was expressed as particle surface area. Specifically, the chronic animal inhalation study of TiO₂ (50) demonstrated the development of lung tumors (bronchioloalveolar adenomas) in response to exposure to a relatively large dose of 250 mg/m³. Subsequently, Henrich et al. (51) showed a statistically significant lung cancer excess in rats exposed to ultrafine TiO₂ at a concentration of 10 mg/m³.

Studies in rats and mice have shown that CNTs and CNFs can pose a respiratory hazard due to pulmonary inflammation and rapidly developing, persistent fibrosis (19, 52). Occupational exposure to CNTs and CNFs has been associated with biomarkers of fibrosis, inflammation, oxidative stress, and cardiovascular responses in workers (53).

**T₂: Effectiveness Research**

Studies conducted under the T₂ stage of the translational continuum are focused on assessing the effectiveness of an intervention. This refers to whether the intervention “works” in the real world outside the laboratory where the conditions are less controlled. Can it protect workers and prevent disease from exposure to TiO₂ and CNT/CNF? And can results from these studies be generalized to other ENM workers/settings?

While not specifically designed as a T₂ study, a cross-sectional study showed that in 12 facilities handling CNT/CNFs that approximately 93% of averaged samples collected at the respirable fraction for EC mass were below the NIOSH REL of 1 μg/m³ (56). This indicates that the REL could be met in practice. No other studies were identified to assess the effectiveness of the NIOSH RELs.

**T₃: Dissemination and Implementation Research**

Dissemination and implementation (D&I) science is defined as the study of methods and strategies for bridging the gap between public health research and practice (13). D&I scientists use a number of empirically tested theories, models and frameworks (TMFs) to plan, evaluate, or understand barriers and facilitators to D&I processes (57–62). Some commonly used TMFs among D&I researchers (63) include the Consolidated Framework for Implementation Research (CFIR) (57), the RE-AIM (Reach, Effectiveness, Adoption,
Implementation, Maintenance) framework and its contextually expanded version the Practical Robust Implementation and Sustainability model (PRISM) (61, 64, 65), the EPIS (Exploration, Planning, Implementation, Sustainment) framework (66, 67), the Diffusion of Innovation theory (68), and the Theoretical Domains Framework (TDF) (69). However, more than 150 D&I TMFs have been identified (70).

In regard to nanotechnology and worker’s health dissemination is the active and targeted distribution of information and intervention materials to a specific business audience. Critical to this is the involvement/engagement with stakeholders early on in the research process so the interventions and strategies for distribution are feasible, relevant, and equitable. Dissemination research is defined as the scientific study of these phenomena for the purpose of understanding how best to spread knowledge required to adopt or deploy an intervention. Implementation of the REL is the critical intermediate step in the continuum from research to prevention. Implementation can be defined as the adoption and integration of evidence-based health intervention (in this case RELs) into business practices.

Implementation research is the study of this process (12). Important translational research questions include what prompts employers to consider the uptake of, and implementation into routine practice and use of such guidance, and what are the key barriers and facilitators to the use of those interventions across diverse workplace settings with different resources (14). D&I science inquiry addresses what works, for who, how, why, in what settings, and how it is sustained over time (34).

Implementation strategies that might be relevant for study include engaging trusted intermediaries and developing a business case.

In the T3 D&I research stage, there are many rigorous study designs that have been used (28, 71). “These include both experimental (e.g., randomized controlled trial, cluster-randomized controlled trial, pragmatic trial, stepped wedge trial, dynamic wait-listed control trial) and quasi-experimental (e.g., nonequivalent groups, pre-/post-, regression discontinuity, interrupted time series), non-experimental or observational (including designs from epidemiology) designs as well as qualitative (e.g., focus groups, semi-structured interviews), mixed-methods (i.e., the collection and integration of qualitative and quantitative data), and system science (e.g., system dynamics, agent-based modeling) approaches” (71). Except for a few qualitative studies, rarely, have any of these study designs been applied to ENM interventions (36).

It appears that there are no published examples of T3 D&I studies related to ENM safety and health so we provide a hypothetical example of questions that could be investigated. Numerous law firms, trade associations, and labor groups served to amplify the REL information published by NIOSH. Translational research in the T3 stage could address what were the best strategies to get the REL information (i.e., intervention) to employers, what are the factors that hinder/facilitate adoption of REL information by employers, how REL information should be packaged and what additional information and resources are needed to facilitate broad dissemination, uptake, and initial implementation by organizations and what are key strategies and resources needed for the sustained use of REL information over time across diverse workplaces. It is critical at this stage and all stages of the research continuum, to consider questions around occupational health equity. These include: how diverse stakeholders including employers, employees labor groups, and professional organizations, will be engaged in the research process and the delivery and implementation of the intervention (i.e., REL information); and will the intervention be feasible for lower resource workplaces employing individuals with high vulnerability?

Measuring success in the T3 stage can take various forms. A possible indicator of success might be to assess the extent to which an intervention, in this case NIOSH guidance, was adopted by companies as the basis for risk management efforts for TiO2 exposure. To make this determination it would be necessary to survey employers on whether they based risk management decisions on NIOSH guidance. However, for such surveys it is difficult to get appropriate participation possibly because the information requested may be viewed as “business confidential”. It may be that tracking the uptake and use of specific guidance may be quite difficult and it might be better to attempt to track uptake of authoritative guidance in general.

Moreover, tracking use of guidance assumes a linear process that a certain authoritative report will influence an employer to take action when clearly employer decision-making is influenced by a large number of factors.

T4: Population Impact

Cross-sectional data shown under the T2 effectiveness stage indirectly demonstrates the population impact of REL information within the population of ENM workers and employers. Although due to the limitations of the design it is challenging to establish a causal pathway between the intervention (REL information) and the observed outcomes of REL usage and exposure control. More data are needed on potential impact of the REL intervention from workplaces where exposure could occur. Also needed are data on the prevalence of control use. There are few studies of the use of controls for ENM interventions in general. Iavicoli et al. (36) found that controls were used substantially but their results were based on a small response rate. This may in part be due to concerns about confidentiality of business information. Ultimately, there is need for studies of the extent of disease in workers over time. Ideally, these would be longitudinal studies or two point in time surveillance assessments (72) and would include diverse process and impact outcomes.

Example 2: WHO Guidance: Protecting From Potential Risks of Manufactured Nanomaterials

T5: Basic Science - Discovery Data

Table 4 illustrates the translational science continuum for this example. In addition to the type of toxicity data discussed earlier for TiO2 and CNT/CNFs, discovery data may be driven from stakeholders’ concerns. For ENMs it was noted in 2007 that “Non-governmental organizations (NGOs) had been active in calling for worker protection
in emerging nanotechnology industries (https://www.who.int/occupational_health/background_review_1.6.12.pdf; line 10).” In 2010 a European Trade Union Confederation recommended application of the precautionary principle because of potential hazards of ENMs. The focus of this example is the WHO guidance on protecting workers from potential risks of manufactured nanomaterials (20). Assessment of the health impacts of new technology is one of the activities of the Global Plan of Action on Worker’s Health adopted in 2007. WHO was concerned that the increased production and use of ENM, meant that workers would be at the “…front line of exposures to these materials placing them at an increased of potential adverse health effects (20).” These guidelines were meant to prevent such effects.

T₁: Efficacy Research
The determination of efficacy of control guidance (i.e., the intervention) was based on years of practice controlling ultrafine particles (6–8). This was supported by evidence-based literature. Specifically, for efficacy of the guidance information created by the WHO workgroup, they used the PECO (Population/Situation Exposure-Comparison-Outcome) approach and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework for the judgement of the quality of the evidence (20). The target group for the guidance was in phase 1: policy makers from low- and medium-income countries and in phase 2, an implementation guide for employers and workers. The policy was designed to fill critical knowledge gaps such as: (1) Can an algorithm be developed to classify engineered nanoparticles by degree of potential hazards? (2) Which characteristics of particles and which measurement techniques should be used for the assessment of exposure to engineered nanoparticles? (3) What is the exposure to engineered nanoparticles in the workplace? (4) What are the limits of engineered controls and personal protective equipment (PPE) with regard to engineered nanoparticles? (5) What occupational health surveillance should be recommended for workers potentially exposed to engineered nanoparticles? (6) Should exposure registries be established for various groups of workers potentially exposed to engineered nanoparticles? (7) Should engineered nanoparticles be treated as “new” substances and evaluated for safety hazards? The guidance was developed by an international group of experts with the assistance of the WHO Global Network of Collaborating Centres who conducted systematic review studies. The guidelines were peer reviewed by external reviewers.

T₂: Effectiveness Research
The effectiveness of the guidance can be assessed against past experience and is similar to the efficacy determination. As noted, one way to assess the effectiveness is through citation analysis. Translation research approaches could be used to determine the extent to which exposure data have been collected in locations where the guidance has been implemented. What was found? No studies on this aspect were identified.

T₃: Dissemination and Implementation Research
The foundation of the D&I stage is the causal evidence that underlies the intervention and the organizational change envisioned. In the WHO guidelines the intervention is recommendations for the safe use of nanomaterials in the workplace.

The WHO Guideline Development Group (GDG) prepared an implementation plan, which included the following activities:
1. Translating to other languages;
2. Integrating the recommendations of the WHO guidelines into training courses on nanosafety (e.g., UNITAR);
3. Providing and disseminating information:
   - web communication;
   - conference presentations;
4. Providing information on the E.U. and U.S. regulations for nanomaterials in the workplace;
5. Developing Safety Data Sheets for nanomaterials in collaboration with the WHO/ILO International Chemical Safety Cards program and UN GHS: nanoscale titanium dioxide (TiO₂) ICSC#1782 and nanoscale zinc oxide (ZnO);
6. Developing a corporate governance document in collaboration with OECD;
7. Developing a list of practical tools for guideline implementation;
8. Assessing the use of nanomaterials in countries;
9. Providing real-world examples on the use of hazard information and proposed OELs in countries and in workplaces.

The GDG started working on the first five activities but did not complete this plan due to competing demands and priorities. Various D&I research studies could examine aspects of the adoption, implementation and sustainment of this plan, however, no studies of the barriers or facilitators in the plan were conducted. This is what would be needed for T₃ stage.

T₄: Population Impact
There are no data to describe the population impact of the WHO report on intermediate indicators such as the use of recommended risk management practices or on ultimate indicators of morbidity or mortality.

Example 3: The International Risk Governance Council (IRGC) White Paper on Nanotechnology Risk
Table 5 illustrates the translational science continuum for this example. The International Risk Governance Council commissioned Renn and Roco to develop a white paper [distilled into a journal article (21)] on a risk governance framework for emerging nanotechnology.

T₅: Basic Science - Discovery Data
The many facets of emerging nanotechnology coupled with many unknowns and extensive societal concerns in the early 2000’s indicated that a comprehensive governance guidance was needed to protect citizens in general and workers in particular who might be at risk. The basic concern was that ENMs may potentially have toxic effects on people exposed to them. The purpose of the IRGC white paper on nanotechnology risk governance was
to present decision makers with a systematic and integrated approach to analyzing and managing anticipated risks from exposure to ENMs (22). While the white paper was expected to have interest to governments, industry, academia, and NGOs, the prime focus was on governments’ responsibility for developing and implementing policies.

There was also concern based on the history of dust explosions that nanoparticles could also be explosive. The white paper stated that, “There seems to be no lower particle size limits below which dust explosions could not occur. It may be possible that the increased surface area of nanoparticles could also include the likelihood that they become self-charged and ignite (22).”

**T₁: Efficacy Research**

T₁ research also involves assessing the potential of the IRGC to recommend risk governance guidance (intervention) (22). An initial scoping workshop involving a broad range of stakeholders and experts from academia, government, industry, insurance, law, and NGOs, was aimed at identifying large governance deficits for nanotechnology. Surveys of experts like those at the scoping workshop were also conducted. These surveys and workshops indicated that industry was highly aware of the potential impact on levels of innovation that could be caused by inadequate risk governance of human health and the environment, and the perception of the public. The major focus identified in the survey responses was research on Environment, Health and Safety and, in particular, the development of guidelines for worker health and safety and the establishment of an international methodology and nomenclature (22).

**T₂: Effectiveness Research**

While many people and groups participated in the development of the IRGC risk guidance this is not necessarily evidence that it is effective. It does support, to some extent, its application potential and acceptance. Translational research could include: synthesis of evidence for risk governance and risk management of fine dust and powders, in particular, as well as efforts to explore applicability of governance guidelines for specific situations. In general, evidence gathering on effectiveness and value of governance could also be accomplished by multi-stakeholder evaluation (73).

**T₃: Dissemination and Implementation Research**

T₃ D&I studies would focus on research on the dissemination and implementation of the IRGC risk guidance. There were no examples in the published literature of T₃ studies for the IRGC risk guidance. In the T₃ stage, assessing the barriers, facilitators, and best practices for the dissemination and implementation of the IRGC risk guidance intervention could be undertaken. For dissemination, one might investigate the extent to which employers and other decision-makers received the governance guidance, what were the best strategies for dissemination, and was there variation in who did and did not receive the guidance (i.e., equity perspective). For implementation, research could focus on how employers adopted, used, and sustained practices based on the IRGC risk guidance.

**T₄: Population Impact**

Like the other examples, the ultimate impact of an intervention is prevention of or decrease in morbidity and mortality associated with the ENM hazard potential. However, the ultimate impact of prevention may take a long time to obtain and the pathway between guidance and prevention may be indirect and involve diverse factors that are difficult to identify. Translational research may need to focus on intermediate outcomes, chiefly utilization of risk assessment and management practices included in the guidance. There were no published examples of T₄ studies for the IRGC risk guidance.

**CONCLUSION**

If occupational safety and health research on ENMs is to lead to protection of workers exposed to ENMs, there is a need to assure that the full continuum from basic research to population impact is considered. Historically, there has not been sufficient focus on the stages that appear “downstream” from basic research. The types of evidence needed and factors and processes associated with these later stages of the continuum can substantially differ from those relevant in earlier stages. Furthermore, these later stages (i.e., understanding what will determine eventual dissemination, implementation, and broad impact of an intervention) can have an important impact on how earlier stages of research (i.e., basic science and efficacy) are done. This paper provides a framework for considering the application of translational science to protect workers exposed to ENMs. Three examples were provided to illustrate this application. The key issues in applying translational science to ENM exposures is the need to invest in such science and the ability to get the results of such research to decision-makers and employers. Translational science may also include explorations of the information uptake and use by employers and decision-makers and identification of barriers and facilitators to these functions.

Clearly, the uptake and use of translational science pertaining to ENMs occurs against a backdrop of societal rules, laws and norms with regard to worker protection. Nonetheless, the outputs of translational science can provide useful information that can lead to the protection of workers. This paper is a call for utilizing translational science on a regular basis. If that is to occur there is need for funding of a workforce with translational science skills. With limited funding for ENM research in general it may be necessary to shift funding for better balance along all phases of the research to impact continuum.

**AUTHOR CONTRIBUTIONS**

PS wrote the first draft. RG and BR made major revisions. TC, LH, and VM provided useful comments and example materials. All authors contributed to the article and approved the submitted version.

**FUNDING**

This was developed as part of government work. PS initiated this paper as part of government work and subsequently under contract.
40. Ponce Del Castillo A. Nanomaterials and Workplace Health and Safety: What Are the Issues for Workers? Brussels: European Trade Union Institute (2013).

41. Fleischer T, Jahnel J, Seitz SB. Technology assessment beyond toxicology – the case of nanomaterials, in responsibility in nanotechnology development. In: Arnaldi S, Ferrari A, Magauda P, Marin F, editors. The International Library of Ethics, Law and Technology. Dordrecht: Springer (2014). p. 79–96.

42. Forlomi G. Responsible nanotechnology development. J Nanopart Res. (2012) 14:1007. doi: 10.1007/s11051-012-1007-1

43. Berube DM. Nano-Hype: The Truth Behind the Nanotechnology Buzz. Amherst: Prometheus Books (2006).

44. Harthorn BH. Nano-buzz: societal dimensions of emerging technologies. Anthropol News. (2006) 47:26. doi: 10.1525/an.2006.47.7.26

45. Tannert C, Elvers H-D, Jandrig B. The ethics of uncertainty: in the light of possible dangers, research becomes a moral duty. EMBO Rep. (2007) 8:392–6. doi: 10.1038/sj.embj.7401072

46. Kurath M. Nanotechnology governance: accountability and democracy in new modes of regulation and deliberation. STI Stud. (2009) 5:87–110. Available online at: https://www.alexandria.unisg.ch/256028/

47. Brownson RC. Bridging research and practice to implement strategic public health science. Am J Public Health. (2011) 111:1389–91. doi: 10.2105/AJPH2011.306393

48. Curry SJ. Organizational interventions to encourage guideline implementation. Chest. (2000). 118(suppl. 2):405–65. doi: 10.1378/chest.118.2_suppl.405S

49. Anderson NB, Orleans CT, Gruman J. Roadmaps for the next frontier; getting the Practical, Robust Implementation and Sustainability Model (PRISM) to integrating research findings into practice. Jt Comm J Qual Patient Saf. (2008) 34:228–43. doi: 10.1016/j.jqrs.2008.03.003

50. Lee KP, Henry NWIII, Trochimowicz HJ, Reinhardt CF. Annual Meetings of the Society of Behavioral Medicine March 3-6, 1999. San Amherst: Prometheus Books (2006).

51. Fleischer T, Jahnel J, Seitz SB. Technology assessment beyond toxicology – the case of nanomaterials, in responsibility in nanotechnology development. In: Arnaldi S, Ferrari A, Magauda P, Marin F, editors. The International Library of Ethics, Law and Technology. Dordrecht: Springer (2014). p. 79–96.

52. Wang L, Davidson DC, Castranova V, and Rojanasakul Y. Pulmonary endpoints for nanomaterials. In: Ferrigno G, editors. Responsible nanotechnology development. Amherst: Prometheus Books (2006).

53. Lee KP, Henry NWIII, Trochimowicz HJ, Reinhardt CF. Annual Meetings of the Society of Behavioral Medicine March 3-6, 1999. San Amherst: Prometheus Books (2006).

54. Wheeler MW, Bailer AJ. Properties of model-averaged BMDs: a study of determinants for implementation outcome. BMC Health Serv Res. (2015) 15:105. doi: 10.1186/s12913-015-0242-0

55. Akaike H. A Bayesian analysis of the minimum AIC procedure. J Clin Epidemiol. (1985) 38:1006–24. doi: 10.1016/S1553-7250(08)34030-6

56. Dahmschroeder LJ, Reardon CM, and Lowery JC. The Consolidated Framework for Implementation Research (CFIR) and the theoretical domains framework (TDF): a systematic review. Implement Sci. (2012) 17:2. doi: 10.1186/s13012-016-0534-2

57. Moullin JC, Dickson KS, Stadnick NA, Rabin B, Aarons GA. Systematic review of the exploration, preparation, implementation, sustainment (EPIS) framework. Implement Sci. (2017) 14:1. doi: 10.1186/s13012-018-0842-6

58. Rogers EJ. Diffusion of Innovations. 5th ed. New York, NY: Free Press (2003).

59. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered building: an international consensus for reporting behavior change interventions. Ann Behav Med. (2005) 3:681–95. doi: 10.1207/s12160-013-9486-6

60. Fiebig M, Rabin B, Glasgow RE. Practical, robust implementation and sustainability model (PRISM) for integrating research findings into practice. Jt Comm J Qual Patient Saf. (2008) 34:228–43. doi: 10.1016/j.jqrs.2008.03.003

61. Lee KP, Henry NWIII, Trochimowicz HJ, Reinhardt CF. Annual Meetings of the Society of Behavioral Medicine March 3-6, 1999. San Amherst: Prometheus Books (2006).

62. Rabin BA, Glasgow RE, Kerner JE, Klump MP, Brownson RC. Dissemination and implementation research on community-based cancer prevention: a systematic review. Am J Prev Med. (2010) 38:443–56. doi: 10.1016/j.amepre.2009.12.035

63. Birken SA, Powell BJ, Pesseau J, Kirk MA, Lorencatto F, Gould NJ, et al. Combined use of the consolidated framework for implementation research (CFIR) and the theoretical domains framework (TDF): a systematic review. Implement Sci. (2012) 17:2. doi: 10.1186/s13012-016-0534-2

64. Schulte et al. Translation Science and Worker Protection