Prudent Precaution in Clinical Trials of Nanomedicines

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I. Introduction

Medical technologies, including nanomedicine products, are intended to improve health but in many cases may also create their own health risks. Medical products that create their own health risks differ from most other risk-creating technologies in that the very purpose of the medical technology is to prevent or treat health risks. This paradox of technologies intended to reduce existing risks that may have the effect of creating new risks has two conflicting implications. On one hand, we may be more tolerant of health risks from medical technologies because these products are intended to, and often (but not always) do, reduce overall health risks and improve our health. The health benefits of a medical technology may outweigh the unavoidable adverse effects of that same technology in an individual patient or in the overall treated population. Even if it turns out that the technology does not improve health overall, we may be willing to accept some failures as the inevitable cost of attempting to deploy new technologies intended and expected to reduce health risks.

On the other hand, we may also be less tolerant of health risks from medical technologies if their very purpose is to reduce health risks, and thus the potential for harm undermines their only reason for existing.[1] Unlike risks in other contexts, such as the environmental risks incidental to producing energy or steel, the risks associated with medical technologies cannot be justified by pointing to non-health related economic or societal benefits from the risk-creating activity. Rather, the potential new risks created by medical technologies must be balanced against the health risks of foregoing a medical technology. The juxtaposition of these two conflicting perspectives to the risk-risk tradeoffs inherent in many medical technologies creates interesting challenges for managing risks, benefits, and uncertainties, and in applying precaution and the precautionary principle.

The precautionary principle, the definition of which will be discussed further below, is a relatively new decision-making tool or approach for addressing risk

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and uncertainty. The application of the precautionary principle is highly contested due to ambiguity about the principle's definition, requirements, and implications, as well as disputed philosophical predicates about the necessity and consequences of the principle. Further refinement and consensus on the meaning and validity of the precautionary principle will likely require exploring its use in specific applications and contexts. Primarily applied by regulators to environmental risks to date, there is no reason the principle cannot also be applied to contexts such as new medical technologies. Nanomedicine provides a potentially useful case study for exploring the precautionary principle, given the novelty of the technology and the large uncertainties about the risks and benefits of the many diverse products and applications of nanomedicine. More specifically, nanomedicine clinical trials provide a new and potentially useful context in which to explore the application, meaning, and value of the precautionary principle. For its part, the precautionary principle may provide a unique perspective for considering the need for added protection of human subjects in nanomedicine clinical trials.

This commentary evaluates the reciprocal questions of whether and how the precautionary principle can enhance the safety of clinical trials for nanomedicines, and what the regulatory challenges presented by nanomedicine clinical trials can teach us about the precautionary principle. Section II elaborates on the precautionary principle and the uncertainties and disagreements about its meaning and merits. Section III analyzes the potential application of the precautionary principle to nanomedicine clinical trial safety. The concluding section then provides some guidance that the precautionary principle offers for nanomedicine clinical trials as well as some lessons that this case study of nanomedicine clinical trials offers for the broader understanding and implementation of the precautionary principle.

II. The Precautionary Principle

Precaution is a fact of life in our modern regulatory state. Science is never certain and final — it is always subject to reconsideration and revision based on new data, findings, and theories. Consequently, science can never identify and quantify a risk with absolute certainty, and some element of precaution is therefore inherent in any regulatory decision that manages these uncertain risks. Two problems have obscured the application of precaution in regulatory decision-making. First, precaution has almost always been applied implicitly and informally rather than explicitly and formally. As a result, there are no criteria, guidelines, or bodies of precedent for applying precaution.[2] Second, there is no consensus on how much precaution should apply to a given problem. Obviously, absolute precaution, in which no activity may proceed unless and until there is absolute certainty of complete safety, is just as implausible as zero precaution, as it would suppress all innovation and invention. Thus, some relative level of prudent precaution is warranted, but there often is strong disagreement about just how much precaution to apply to a given risk scenario. In particular, there is no agreement on questions such as: How much and what kind of evidence is sufficient to trigger precautionary action? How much and what kinds of risk and uncertainty are acceptable? How should costs and benefits be balanced against risks, if at all?

The precautionary principle addresses the first problem above but not the second. It makes consideration of precaution an open, express, and often mandatory factor in a regulatory decision. But the precautionary principle does not resolve the second problem of determining how much precaution is appropriate. The precautionary principle is now a manda-

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tory requirement of the treaty creating the European Union and has also been adopted into the national laws of many individual European governments. The principle has been incorporated into over 50 international agreements and adopted legislatively or by the courts in many other jurisdictions ranging from nations such as India and Canada to cities such as San Francisco and Seattle.[3] Yet, no standard formulation of the precautionary principle exists.[4] Every jurisdiction that has enacted the precautionary principle to date has simply adopted "the" precautionary principle without defining or citing to any definition of the principle.[5] There are numerous semi-official and informal definitions of the precautionary principle floating around, but they have no legal binding effect and they vary among themselves significantly.

For example, consider the two most popular formulations of the precautionary principle. First, the Rio Declaration on Environment and Development issued in 1992 by the United Nations Conference on Environment and Development (UNCED) defined the principle as follows: "Where there are threats of serious and irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."[6] This version of the precautionary principle, which is the only version the U.S. government has endorsed, has been referred to as the "wimpy" version of the principle.[7] A much stricter definition, known as the Wingspread Statement, was developed by several prominent supporters of the principle: "When an activity raises threats of harms to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."[8] These two popular versions differ significantly, such as whether they apply to risks of "serious and irreversible damage" or apparently any risk, whether they are permissive or obligatory, and whether solutions are required to be cost-effective or not. Other semi-official versions of the precautionary principle differ in even more ways.[9]

But perhaps even more significant than the lack of a consensus or formal definition and the variation between the unofficial versions of the precautionary principle is that no existing formulation of the precautionary principle answers key risk management questions, such as: How substantial must a potential risk (or risk uncertainty) be for the precautionary principle to apply? What level of risk is acceptable? What early indications of potential hazard are needed to trigger precaution? How much data must be produced to demonstrate that a product is "safe"? How are costs, and the tradeoffs presented by technologies that may simultaneously reduce and create different risks, factored into precautionary decision-making, if at all? What action is required to satisfy the precautionary principle when it does apply?[10]

The European Commission tried to better define and develop the precautionary principle in a 29 page "Communication" released in 2000.[11] In that document, the Commission stated that the precautionary principle is a risk management rather than risk assessment tool, to be employed to manage risks after a scientific risk assessment has already identified the risks and uncertainties associated with a product.[12] Moreover, risk management decisions utilizing the precautionary principle must be proportional, in that they weigh the costs and benefits of the product, and also non-discriminatory, in that they do not selectively single out certain products or technologies for disparate treatment.[13] The Communication failed to address other critical questions, however, such as what level of risk is acceptable and what kinds of evidence of risk are necessary to trigger the application of the precautionary principle, leaving those as political decisions.[14] But even this limited articulation of the precautionary principle was controversial, as other supporters of the precautionary principle believed it should apply at the risk assessment, not risk management stage,[15] and other proponents rejected the Commission's embrace of cost-benefit analysis under the principle.[16]

We are thus confronted with a precautionary "principle" that is legally mandated in many nations and jurisdictions but which remains under-defined and under-developed. The consequence is that the precautionary principle is applied in an arbitrary, unprincipled, and sometimes absurd manner.[17] It becomes particularly problematic to apply the precautionary principle to technologies such as those in the medical field that present both health risks and health benefits.[18] For example, how would the precautionary principle apply to clinical trials of potentially beneficial medical products? These products usually are intended to provide important safety benefits, though yet unproven, while at the same time the product may inflict new risks, which again are highly uncertain at early clinical trial stages. The balancing of these uncertain risks and benefits of clinical trials is already the focus of an extensive set of regulations and procedures for the protection of human subjects, but often new technologies, and most recently nanomedicine, have sparked calls for additional protections over and beyond the existing general human research subject protections.[19]

Does the precautionary principle help us to decide whether and how nanomedical products might warrant additional safety protections during clinical

testing? If the precautionary principle is applied to only consider the risk side of the equation, as often seems to be the case, it "would prohibit the majority of clinical trials, because it holds that when decision-makers lack sufficient knowledge about the effects of a potentially dangerous activity, one should not proceed."[20] If applied strictly, therefore, the precautionary principle would ban most medical innovation, a result clearly inconsistent with the public's health and welfare. As Cass Sunstein has written, "[T]he precautionary principle, for all its rhetorical appeal, is deeply incoherent. It is of course true that we should take precautions against some speculative dangers. But there are always risks on both sides of a decision; inaction can bring danger, but so can action. Precautions, in other words, themselves create risks – and hence the principle bans what it simultaneously requires."[21] The clinical trial example thus suggests that a more nuanced and prudent precautionary approach is needed.

To further articulate and operationalize a practical and realistic precautionary principle, the way forward will likely require examination of contextual case studies that may justify some application of precaution, and to try to identify a prudent role for precaution in specific contexts. For the reasons alluded to above, clinical trials of nanomedicine products may provide a useful case study to explore the appropriate application of precaution and meaning of the precautionary principle.

III. Applying Precaution to Nanomedicine Clinical Trials

Clinical trials of nanomedical products provide a specific case study for exploring application of precaution and the precautionary principle with some granularity. In examining applications of the precautionary principle to any specific risk scenario, two broad questions must be considered: (1) what are the factors for and against applying precaution (or a specific degree of precaution) to that specific risk scenario; and (2) what risk management strategy or changes to the status quo does the application of the precautionary principle require if it is applicable?

Arguments For and Against Precaution

FOR PRECAUTION

On the first question, there are several possible factors that might argue in favor of applying a significant modicum of precaution to nanomedicine clinical trials. Nanotechnology products might present a greater risk in general than non-nanotechnology products.[22] Nanomaterials tend to be relatively more active than their bulk comparators due to their greater relative surface area, which increases the potential for reactivity, as well as their unique quantum effects, which increase the energy level of nanomaterials.[23] Notwithstanding these differences, most scientists and scientific and regulatory bodies have not (at least not yet) concluded that nanomaterials as a category present greater risks than non-nano products.[24] For example, the Food and Drug Administration (FDA) created an internal Task Force on nanotechnology which concluded that "[t]he available information does not suggest that all materials with nanoscale dimensions will be hazardous. Furthermore, if all nanoscale materials are compared to all non-nanoscale materials, whether larger or smaller, it is not apparent that the nanoscale materials as a group would have more inherent hazard."[25] Expressing a similar sentiment, the FDA Commissioner wrote in April 2012 that "FDA does not categorically judge all products containing nanomaterials or otherwise involving the application of nanotechnology as intrinsically benign or harmful."[26] In a June 2011 memorandum to federal agencies, the White House likewise instructed agencies to "be careful to avoid actions that could improperly characterize nanomaterials as inherently hazardous or benign."[27] Notwithstanding these reservations, if nanomedical products are indeed found to present greater risks than conventional medical products, that finding would argue for applying more precaution to nano clinical trials. In the absence of such a conclusion, however, this factor does not necessarily weigh in favor of applying more precaution.

The complexity and potential for over-reaction to the word "nanotechnology" — whether it be unwarranted negative stigma or unjustified positive therapeutic misconception — will further challenge the informed consent process. Thus, these factors may argue for greater precaution — either in the form of greater care in the informed consent process itself, or for greater protections that might compensate for the limitations of the informed consent.

Even if nanotechnology products are not riskier than non-nano products generally, they likely present greater uncertainties about risk.[28] Nanomaterials have the potential to act by unique mechanisms and routes of exposure (e.g., bypassing the blood-brain barrier), and moreover their potential to cause harm is harder to predict since their hazard potential is determined by factors such as surface area, rather than molecular structure which is used to predict the risks of most other chemical hazards.[29] Furthermore, there are not proven toxicity screening assays or methods to evaluate the risks of nanomaterials.[30] Moreover, pre-clinical studies of nanodrugs using animals may be less predictive for human risk than traditional chemical drugs due to the novel mechanisms that may be involved in nanotechnology toxicity.[31] The greater uncertainty associated with nanotechnology risks weighs in favor of applying more precaution to these products.

Another factor that might weigh in favor of greater precaution relates to a distinctive element of clinical trials: the need for informed consent from research subjects. Trials involving nanomedicine may present unique challenges to obtaining truly informed consent. The greater uncertainty about the risks (and benefits) of nanomedical products challenges the informed consent process because subjects cannot truly consent to risks that are largely unknown or highly uncertain, although there are mechanisms to help research subjects understand and decide whether to accept the uncertainties. Moreover, the complexity and potential for over-reaction to the word "nanotechnology" — whether it be unwarranted negative stigma or unjustified positive therapeutic misconception — will further challenge the informed consent process.[32] Thus, these factors may argue for greater precaution — either in the form of greater care in the informed consent process itself, or for greater protections that might compensate for the limitations of the informed consent.

Finally, more precaution might be justified by the greater public anxiety and concern about nanotechnology products. One of the oft-cited precepts of the precautionary principle is the need to give greater weight to public perceptions and opinion.[33] Thus, if the public is more concerned about medical products that employ nanotechnology than those that do not, arguably greater precaution would then be justified for the nano products. Moreover, if adequate precaution is applied and the clinical trials of nanomedicines result in a serious injuries to research subjects or bystanders, the impact would be devastating on the entire nanomedicine industry. Media and activist attention would sharply criticize all nanotechnology, resulting in new barriers and reluctance by many companies to proceed with nanomedicines. For this reason, it is in everyone's interest to ensure that appropriate precaution is applied to minimize the risk of a harmful event, both to the research subject who will incur the physical harm, and the broader industry which could be harmed by consumer or media backlash against its products.

AGAINST PRECAUTION

There are also influential factors against applying extra precaution to clinical trials involving nanotechnology. First, many nano medicines have the potential for important therapeutic benefits. Nanomedicines are likely to be one of the most beneficial applications of nanotechnology, with many innovative products such as targeted anti-cancer agents showing great promise.[34] Delaying or impeding the development of such beneficial products by excessive precaution in the form of enhanced regulation of clinical trials may do more harm than good to human health.[35] As one set of prominent nanomedicine experts warned: "[C]areful scrutiny of potential safety risks is absolutely necessary — yet the greatest risk in nanomedicine may well be in letting our concerns paralyze our action and not taking advantage of the full, revolutionary potential that nanotechnology in medicine can offer humankind."[36]

Another problem for applying precaution generically to all nanomedical products is the tremendous variety and heterogeneity of nanotechnology materials and applications.[37] There are a "staggering number" of different engineered nanomaterials being developed for medical and other applications.[38] For example, over 50,000 different types of carbon nanotubes alone are possible.[39] These many different types and uses of nanomaterials will likely present a wide variety of different risk scenarios, with each nanomaterial requiring its own individual assessment, at least until more information is known to allow some categorical extrapolations for classes of nanomaterials.[40] Accordingly, applying a generic precautionary assumption at this time would likely be a blunderbuss and unwarranted strategy.

There are also more practical impediments to applying precaution selectively to nanomedical products. One is the difficulty of defining nanotechnology with precision so as to clearly differentiate those medical products that are "nano" and thus subject to the extra precaution from those products that are not nano. The FDA has to date declined to offer a specific definition of nanotechnology.[41] There are good reasons for the lack of a definition. While nanomaterials are generally regarded as being in the range of 1 to 100 nanometers in size, virtually any product contains some particles in that size range.[42] It then becomes necessary to define what percentage of the particles in the product

must be in the nanoscale size range for the product to count as "nano," a very problematic and subjective requirement to both define and enforce. Moreover, the definition must account for the dynamic changes in many products — for example, most active ingredients in drugs, whether considered nano or not, pass through the nanoscale size range at some point in their absorption, distribution, metabolism, and excretion. As the FDA has noted, "[E]very degradable medical device or injectable pharmaceutical generates particulates that pass through this [nano] size range during the processes of their absorption and elimination by the body."[43] A further complication is that some argue that a nanotechnology definition must go beyond a size requirement and include only nanoparticles that exhibit size-related special properties, yet defining and measuring those properties is problematic if not infeasible.[44] Thus, because the application of extra precaution to nanomedicine is contingent on the capability to clearly define which products encompass nanotechnology, the absence of a workable definition weighs against the feasibility of special precautionary requirements for nanomedical products.

products. Nonetheless, the fact that there are two separate institutional reviews (IND and IRB) focused on the safety of research subjects prior to commencement of the clinical trial reduces the need for additional precaution to some extent.

Finally, singling out nanomedicines for special precautions would likely unfairly stigmatize nanotechnology products. Discriminatory regulatory burdens lacking scientific rationales have the potential to tilt the playing field and lead to inefficient and counterproductive results.[47] Companies would have harmful incentives to avoid disclosing the nanotechnology ingredients of their products or to substitute less effective non-nano materials in order to avoid the regulatory burdens and the associated stigma of the nano-specific requirements. Furthermore, empirical data suggests that subjecting a product to the precautionary principle may inflame rather than calm public concerns and anxiety about that product, and thus any strategy to build public confidence by applying more precaution may backfire.[48]

Sensible application of the precautionary principle to nanomedicine clinical trials, if warranted at all, would therefore call for more limited and modest additional protections. Several possibilities exist.

Another factor weighing against application of the precautionary principle to clinical trials of nano products is the significant safety cautions and protections already applied to all clinical trials, including trials of nanomedicines. The safety of nanomedicines that are commercially marketed is the responsibility of the FDA, both during the early clinical trials through the Investigational New Drug (IND) approval process, as well immediately prior to and after marketing through the FDA new drug approval process. Further protection for research subjects is provided by the FDA human subject protection regulations, which among other things require informed consent and approval of trial protocols by the local Institutional Review Board (IRB).[45] The IRB applies a version of the precautionary principle in effect if not in name by typically erring on the side of safety to protect research subjects.[46] While these FDA IND and the IRB approvals provide some protection to research subjects, the FDA regulations and the expertise of the IRB are unlikely to be attuned to any special risks or uncertainties associated with nanomedicines, so there is no assurance that the existing review mechanisms will be adequate for these

Precautionary Policy Choices

As shown in the previous subsection, there are pros and cons of applying extra precaution to clinical trials involving nanomedical products. The balance of these factors does not seem to tilt overwhelmingly either in favor of or against applying additional precaution, illustrating the subjective nature of such a decision. Nevertheless, if additional precaution were to be applied, there are several ways in which it could be applied to nanomedicine clinical trials. It is first worth noting, however, that the second question of *how* precaution should be applied is not independent of the first question of *whether* additional precaution is warranted. Here, where the argument for additional precaution is equivocal at best, any additional precautionary measures that are selected should be tempered and not unduly burdensome.

The most extreme application of precaution to nanomedicine clinical trials would be to prohibit such trials altogether until more is known about the risks of nanotechnology. Some organizations have relied on the precautionary principle to call for a moratorium on all uses of nanotechnology, including medical uses,

until they can be demonstrated to be safe.[49] Given that it is impossible to prove the absence of risk, combined with the fact that no product is absolutely safe in all contexts, any such demands to prove absolute safety are unrealistic and irresponsible, and cannot be what the precautionary principle requires if it is to have a serious role in regulatory policy. As one European judicial opinion noted, the "precautionary principle has a future only to the extent that, far from opening the door wide to irrationality, it establishes itself as an aspect of the rational management of risks, designed not to achieve zero risk, which everything suggests does not exist...."[50] While prudent application of the precautionary principle may require that certain high-risk products be withheld until further information on safety is available (recognizing that there will always be limitations to such data), such harsh restriction would be inappropriate for nanomedical products as a category given their potential to provide substantial health benefits.

Sensible application of the precautionary principle to nanomedicine clinical trials, if warranted at all, would therefore call for more limited and modest additional protections. Several possibilities exist. One measure would be to revise the trial design to only allow diseased subjects who might benefit from such products to participate in clinical trials. Most Phase I trials of medical products involve healthy subjects in which the therapy is tested for safety, without any possibility of benefit (given that the subjects do not have the underlying condition that the product is intended ultimately to treat). In some trials, such as those involving some harsh cancer drugs, it is unethical to give the drugs to healthy subjects because of an unacceptably large risk of serious side effects. Accordingly, such studies are limited on ethical grounds only to sick patients who might possibly benefit from the treatment.[51] Likewise, if sufficient concerns and uncertainties exist for nanomedicines, it may be prudent under the precautionary principle to limit such trials to diseased patients who could potentially benefit from the treatment, and thus more likely justify the associated risks and uncertainties.[52]

Other precautionary measures could be implemented to make nanomedicine trials more protective of the safety of research subjects. More frequent or thorough health monitoring of trial participants could be required during clinical trials of nanomedicines. Data and safety monitoring boards (DSMBs), normally only required in limited circumstances such as phase 3 and multi-site trials, could be required more frequently for nanomedicine clinical trials, and the DSMBs could adopt stricter rules for stopping trials when there are early indications of potential hazards.[53] Precautionary measures can also include additional data gathering or monitoring requirements to ensure safety, such as a requirement for post-trial monitoring for nanoproducts to help detect any latent or slow-developing health effects. Nanomedicines could require more pre-clinical studies in animals compared to non-nano medicines, as well as additional studies in human cell lines given the potentially greater species' differences in response associated with nanotechnology.[54]

Additional measures might include requiring lower initial doses or using fewer subjects in Phase I trials in order to minimize the likelihood of harm to the first human subjects exposed to the nanomaterial. The treatment could be tested initially in a "microdose" study, sometimes referred to as a Phase 0 study, in which a small number of subjects (<10) are given a dose in the range of 1/100 the pharmacologically effective dose for just one week in order to look for any early warning signs of toxicity.[55] Similarly, the three phases of clinical trials could be staggered more slowly to allow longer follow-up periods between Phase 1 and Phase 2 or between Phase 2 and Phase 3. More or larger studies could be required in Phase 3 to increase confidence in experimental nanomedicines before they are given final approval for widespread use.[56]

Various types of extra oversight by additional institutions could be another way to add more precaution to nanotechnology clinical trials.[57] The Recombinant DNA Advisory Committee (RAC), for example, was created to provide additional oversight and transparency regarding controversial gene therapy protocols beyond that provided by local IRBs and the FDA.[58] Following this model, a new or existing federal-level advisory board could be established to evaluate clinical trials of nanomedical products.

An additional area for more precaution could be an enhanced informed consent process. That might include providing more information and longer consultations with prospective trial participants to ensure they understand what is known and unknown about the nanomedicine being tested. Longer waiting periods could be required between the initial consultation and enrollment in a trial in order to ensure research subjects have not been too hasty in agreeing to participate in trials. Simply disclosing to research subjects that the test material they are being treated with involves nanotechnology could be understood as modest precaution because it may give the subjects more information to make informed choices about what risks they undertake. On the other hand, research subjects might have an inflated conception of what nanotechnology medicines are capable of (therapeutic misconception), or alternatively might have an unjustified alarmist fear of nanotechnology (malevolent misconception),[59] so it is

unclear whether disclosing the nanotechnology nature of a treatment would be precautionary.

IV. Conclusion: Observations and Lessons

This brief exploration of the potential role of the precautionary principle in providing greater safety in nanomedicine clinical trials, and how that inquiry is fraught with inherent complexities, uncertainties, and subjectivity provides some broader observations and lessons for both nanomedicine clinical trials and for the precautionary principle.

Implications for Nanomedicine Clinical Trials

The often competing goals of promoting the benefits of nanomedicine and ensuring that human trials of such products are safe create a tension. Additional measures to promote the safety of research subjects have the potential to slow and strain the development of promising new nanotherapeutics, perhaps to the detriment of public health. On the other hand, rushing products through the evaluation and approval stages without sufficient care and consideration of the safety of the research subjects not only generates ethical concerns but may also provoke a backlash against nanotechnology if some research subjects are harmed. In addition to this fundamental tension between innovation and safety, there are additional concerns in potentially stigmatizing nanotechnology by requiring additional precautions for nanomedicine clinical trials relative to trials for other types of products. Finally, the enormous variety and heterogeneity of nanotechnology products in a field such as medicine, as well as the challenges in precisely defining nanotechnology, demonstrate the difficulty and perhaps futility of trying to design specific precautions for this field of nanomedicine as a whole.

It is hard to draw strong conclusions from this very tangled mix of considerations, other than that some modest safety improvements to human subject protection may be warranted in nanomedicine clinical trials to enhance both the actual and perceived safety of the trials, provided they do not unduly burden, stigmatize, or delay promising nanomedicine products and applications. Ideally, because any clinical trial can produce unexpected risks, such minimally-burdensome enhancements to safety should be implemented for all medical products, not just nanomedicines. In the absence of any across-the-board reforms, though, an extra dash of precaution in nanomedicine clinical trials may be warranted by the fact that the public and media are likely to perceive any harms from a nanotechnology product as applying to all nanotechnology products. By bringing greater visibility and prominence to the implications of potential risks, uncertainties, and public perceptions in this and other contexts, prudent application of the precautionary principle may be able to help to identify and assess innovative policy prescriptions.

Implications for the Precautionary Principle

The nanomedicine clinical trials case study demonstrates how subjective and idiosyncratic the application of the precautionary principle must be, at least at the present time. In this case study of nanomedicine clinical trials, the regulatory context and consequences, risk-benefit tradeoffs, uncertainties, and specific potential precautionary steps that are possible require a customized and unique consideration of how and where additional precaution may and should apply. This highly contextualized inquiry defies any generic rules or guidelines that could sensibly apply simultaneously to this and the many other risk scenarios in which the precautionary principle could potentially be applicable. One clear lesson is that blunt prescriptions such as automatically banning or blocking a technology or activity so long as some risk uncertainty remains would be highly problematic and counter-productive. Rather, precaution and, to the extent it is to be applied prudently, the precautionary principle, must for the foreseeable future be applied at the retail rather than wholesale level. Each risk situation must be considered in its context, necessitating a careful, balanced, nuanced, and (unfortunately) subjective exploration of how and where precaution may be applied to do more good than harm.

This finding raises serious questions about the overall usefulness and role of the precautionary principle. To the extent that the principle can be applied in a moderate manner, as a vehicle for raising the question of what level of precaution is appropriate in a given circumstance, the precautionary principle may serve a useful function. Even then, though, the moderate implementation of precaution may be little different than, and collapse into, the existing regulatory approaches,[60] except perhaps for making the application of precaution somewhat more transparent. For example, the question of what level and types of protection should apply to nanotechnology clinical trials proceeds, as demonstrated by the other articles in this special issue, without recourse to the precautionary principle. At most, the precautionary principle provides a background norm pushing in the direction of greater protection, but without providing any specifics on the types or amount of protection that should be provided. Alternatively, if the precautionary principle is applied in its more extreme form as a knee-jerk weapon to block specific products or technologies for political or protectionist reasons, as unfortunately

often seems to have been the case to date,[61] the precautionary principle itself may do more harm than good.

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