REGULATORY CHALLENGES OF SYNTHETIC BIOLOGY TRIALS AND OTHER HIGHLY INNOVATIVE INVESTIGATIONAL PRODUCTS

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While synthetic biology remains in the early stages of innovation, achieving its posited goal of improving human health will depend on future clinical trials. This article raises questions about Australia's capacity to ensure that clinical trials involving these kinds of highly innovative investigational products have an acceptable initial and ongoing risk-benefit ratio. Particular challenges include scientific uncertainty surrounding the risks and benefits posed by highly innovative investigational products, as well as the normative nature of assessments of their likelihood and magnitude. These difficulties are compounded by a lack of substantive standards for judging the acceptability of identified trial risks in light of the trial's potential benefits. In Australia, the Office of the Gene Technology Regulator, the Therapeutic Goods Administration, and Human Research Ethics Committees will share responsibility for assessing risks and benefits for participants in future synthetic biology clinical trials. The article argues that none of these bodies — as they currently operate — are equipped to undertake such reviews and canvasses strategies for better supporting them in this role.

I INTRODUCTION

The past century has witnessed science fiction become reality across a gamut of medical innovations: vaccines, dialysis machines, and organ donations exemplify leaps of clinical science that have translated into remarkable health benefits. In the 1980s, attention turned to genetic sequencing and transfer, and associated 'omics' technologies, the benefits of which are starting to permeate clinical practice. Synthetic biology — the application of engineering techniques to biology to create organisms or biological systems with novel or specialised functions[1] — is gaining prominence for its potential to transform medicine in the future. Although most clinical applications remain some way into the future,[2] advances such as the creation of the world's first self-replicating synthetic genome,[3] and in 2014 the first eukaryotic chromosome,[4] highlight the rapid pace of scientific discovery. No doubt the 'century of biology'[5] will generate currently unimaginable technologies that further shift traditional paradigms of clinical research and practice.

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1 The Presidential Commission for the Study of Bioethical Issues, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (The Presidential Commission for the study of Bioethical Issues, 2010) 2 <http://bioethics.gov/synthetic-biology-report>.

2 Ibid 67.

3 Daniel G Gibson et al, 'Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome' (2010) 329 *Science* 52.

4 Narayana Annaluru et al, 'Total Synthesis of a Functional Designer Eukaryotic Chromosome' (2014) 344 *Science* 55.

5 Craig Venter and Daniel Cohen, 'The Century of Biology' (2004) 21 *New Perspectives Quarterly* 73.

Highly innovative products and techniques provide dramatic promise for medical progress, often raising pressure to commence clinical testing speedily. Yet early uses in clinical trials can involve unforeseeable risks. The death of 18-year old Jesse Gelsinger in a 1999 gene therapy trial from an unexpected inflammatory reaction to the gene-transfer vector is well known, with news of the death and the resulting lawsuit dealing 'a major blow for the gene therapy community'.[6] In the following couple of years, excitement about initially promising reports of successful gene-therapy treatments for children suffering from an immune-deficiency disease turned to alarm when two of the ten treated children developed a leukaemia-like lymphocyte proliferation.[7] Subsequent gene therapy studies have obtained some promising results, and the first gene therapy product has been approved for clinical use in China (albeit with some consternation about the data used to support approval); however, much remains to be learnt about the safety profile of different gene vectors.[8] In this and other emerging technology fields, navigating the competing demands of facilitating clinical testing and translation, while minimising risks to research participants, requires proactive regulatory attention.

This article identifies the challenges of ensuring the ethical acceptability of clinical trials involving highly innovative investigational products – most notably, determining a favourable risk-benefit ratio. Using synthetic biology as an illustrative case study, it goes on to assess the capacity of Australia's regulatory systems to assess the risks and benefits of future clinical trials. After concluding that there are considerable gaps in protections, the article suggests options for reforming Australia's regulatory frameworks for clinical trials with highly innovative investigational products.

II SYNTHETIC BIOLOGY AS A HIGHLY INNOVATIVE INVESTIGATIONAL PRODUCT

The National Statement on Ethical Conduct in Human Research ('National Statement') — guidelines developed for researchers working with human subjects in Australia — defines a clinical trial as 'a form of human research designed to find out the effects of an intervention, including a treatment or diagnostic procedure'.[9] This covers a broad spectrum of activities, ranging from the first administration of a completely novel substance to humans through to efficacy and safety comparisons of well-characterised therapeutics. To help address this diversity, clinical trials traditionally have been categorised into various 'phases'. Phase I studies involve the first administration of an investigational product to humans to determine the product's safety and pharmacological activity at various dose levels. In Phase II trials, an investigational product is administered to people with the health condition for which the medicine is intended to provide preliminary evidence of efficacy and safety. If Phase II studies show potential benefits, the investigational product will be tested in larger and lengthier Phase III trials to assess whether the product confers a sufficient clinical benefit to warrant marketing approval. Phase IV trials are conducted after a product has been approved for marketing to further explore the clinical use of the medicine.[10] More recently, drug regulators have recognised an additional trial phase: Phase 0. This encompasses exploratory, first-in-human trials conducted before traditional dose escalation and safety studies in order to establish whether the drug or agent behaves in human subjects as had been anticipated from preclinical studies.[11]

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6 Michael L Edelstein, Mohammad R Abedi and Jo Wixon, 'Gene Therapy Clinical Trials Worldwide to 2007 — an Update' (2007) 9 *The Journal of Gene Medicine* 833, 834.

7 Ibid.

8 Edelstein, Abedi and Wixon, above n 6.

9 Australian Government National Health and Medical Research Council, *National Statement on Ethical Conduct in Human Research* (2007) 3.3.

10 Ibid 30–31.

11 National Health and Medical Research Council, *Certification Handbook: National Certification Scheme of Institutional Processes Related to the Ethical Review of Multi-Centre Research*, 10 <hrep.nhmrc.gov.au/_uploads/.../hrep_certification_handbook_2012.pdf>.

This article focuses on the earliest part of this clinical pathway: Phase 0 and I trials involving the first administrations of an investigational product to humans. In particular, it assesses strategies to regulate the first administration of highly innovative investigational products to humans: that is, investigational products where

> the biological mechanisms are not fully understood, animal models do not reliably predict human effects, adverse effects cannot be minimized by starting with a low 'dose', and the interventions have never or only rarely been previously used in humans.[12]

Future synthetic biology trials are likely to provide an archetypal example of highly innovative investigational products. Consider, for example, a mouse study involving implantation of a cell engineered to produce a synthetic genetic signalling cascade in response to a licensed antihypertensive drug (guanabenz). This combination of drug- and gene-based therapies allowed guanabenz to dose-dependently control hormone expression, simultaneously ameliorating the pathologies that constitute metabolic syndrome (hypertension, hyperglycaemia, obesity and dyslipidaemia).[13] Should such a technique be translated into clinical trials, it would involve uncertainty as to the full biological mechanisms, questions about the reliability of mouse models for predicting effects of the engineered cell in humans, and a lack of previous experience with similar interventions. It is unlikely that these uncertainties could be mitigated through reliance on a low dose. Similar challenges arise with other potential future examples of synthetic biology research, including the use of synthetic T-cells to kill targeted patient cells (such as cancer types) and the administration of genetically recoded viruses for vaccination.[14]

III AUSTRALIAN REQUIREMENTS FOR ETHICAL ACCEPTABILITY OF HUMAN RESEARCH

Numerous national and international guidelines specify that trial sponsors, investigators, and institutions must ensure the ethical acceptability of clinical trials for which they are responsible.[15] While the scope and drafting of these guidelines differ, commentators have distilled seven requirements as the core conditions necessary for ethical acceptability: the research must have potential value; the methodology must be scientifically valid; participants must be selected fairly; the research must have a favourable risk-benefit ratio; review of the research must have been provided by an independent body; participants must have provided informed consent; and participants must be accorded respect, including the opportunity to withdraw.[16]

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12 Bernard Lo and Deborah Grady, 'Strengthening Institutional Review Board Review of Highly Innovative Interventions in Clinical Trials' (2009) 302 *JAMA* 2697. This definition is broadly consistent with the definition of 'high risk' investigational products set out by the European Medicines Agency, which notes that concerns may be derived from the novelty of a product's mode of action, the extent of available knowledge about a product's target, and the questionable relevance of animal models: European Medicines Agency, 'Guidelines on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products' <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000400.jsp>.

13 Haifeng Ye et al, 'Pharmaceutically Controlled Designer Circuit for the Treatment of the Metabolic Syndrome' (2013) 110 *Proceedings of the National Academy of Sciences* 141.

14 Florian Lienert et al, 'Synthetic Biology in Mammalian Cells: Next Generation Research Tools and Therapeutics' (2014) 15 *Nature Reviews Molecular Cell Biology* 95.

15 Australian Government National Health and Medical Research Council, above n 9; World Medical Association, 'World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects' (2013) 310 *Journal of the American Medical Association* 2191; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 'Guideline for Good Clinical Practice E6 (R1)' <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf>.

16 Ezekiel J Emanuel, David Wendler and Christine Grady, 'What Makes Clinical Research Ethical?' (2000) 283 *Journal of the American Medical Association* 2701.

Highly innovative investigational products test many of these ethical preconditions. The technicality of the product information can make it hard to obtain meaningful informed consent. The often-acute illness of the population being recruited can raise questions about fair subject selection. The small cohort of people with the requisite scientific knowledge can impede the potential to obtain a review by a completely unaffiliated individual. Each of these issues is worthy of dedicated consideration. For the most part, however, the strategies for promoting the ethical acceptability of trials involving highly innovative investigational products will mirror strategies developed in the context of clinical trials more generally (albeit with potentially more serious consequences). Yet, for reasons explained in following sections of this article, one ethical precondition poses particular challenges in the context of highly innovative investigational products: ensuring a favourable risk-benefit assessment.

IV CHALLENGES OF RISK ASSESSMENT FOR HIGHLY INNOVATIVE CLINICAL TRIALS

A favourable risk-benefit ratio for a clinical trial requires a preliminary and ongoing judgment that the trial's potential benefits to individual participants and/or society are proportionate to or outweigh its risks.[17] In Australia, the National Statement specifies that a trial's benefits may include 'its contribution to knowledge and understanding, to improved social welfare and individual wellbeing, and to the skill and expertise of researchers'.[18] The National Statement further provides, in the context of clinical trials, that:

> In research without any likely benefit to participants, any known risk to participants should be lower than would be ethically acceptable where there are such likely benefits. In 'first-time-in-humans' research projects, risks are uncertain, and recruitment into the study should therefore be gradual and monitored with special care.[19]

Yet scholars are increasingly recognising the complexity of making any such determination, particularly when it comes to highly innovative investigational products, given the following:

- The risks and benefits are often unclear.
- Assessments of the likelihood and magnitude of risks and benefits are context-dependent and steeped in broader moral and social judgments.
- Once the relevant risks and benefits have been identified, there is no agreed framework for weighing them or substantive standards for assessing their acceptability.

A *Unclear Benefits and Risks*

Highly innovative investigational products, such as those likely to arise through synthetic biology, by definition involve unclear benefits and risks. Extrapolating from the gene therapy context, the likelihood of clinical benefits accruing to individual participants is low. Only a handful of the 1,340 gene therapy trials conducted since 1989 have reported positive results,[20] an unsurprising finding given the breadth of uncertainty about the causal pathways necessary for clinical success. The most realistic benefits therefore involve the generation of scientific knowledge. However, ascertaining such value requires considerable expertise. Gene therapy research once again poses a cautionary tale. A 1995 report commissioned to provide recommendations to the National Institute of Health ('NIH') in the US raised concerns about the limited potential to extrapolate 'useful basic information' from the majority of gene

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17 Ibid.
18 Australian Government National Health and Medical Research Council, above n 9, 1.1(a).
19 Ibid 3.3.7.
20 Edelstein, Abedi and Wixon, above n 6.

therapy studies because of experimental design deficiencies.[21] The authors further noted that an 'enthusiasm to proceed to clinical trials' meant that inadequate attention had been given to 'basic studies of disease pathophysiology', which were likely to be critical to the field's future success.[22] These same dynamics are likely to emerge in synthetic biology and other highly innovative investigational products.

Quantifying the likelihood that an early-phase trial will harm participants (that is, the risks of an early-phase trial) is also hard. There is limited evidence quantifying harms resulting from participants in early phase research, [23] with some studies showing that the preponderance of such trials incur only minor adverse events.[24] However, fears about the potential risks associated with such trials have been raised by catastrophes such as the death of a healthy volunteer in a Phase I asthma study,[25] as well as the TeGenero incident in the United Kingdom, in which a Phase I trial of a monoclonal antibody led to systemic organ failure in six participants.[26] While the risks of early phase trials are typically estimated and minimised through research with animal models, these can have limited predictive ability — as evidenced in the TeGenero trial.[27] The lack of reporting requirements for early-phase trials further limits our knowledge base on adverse event rates and grades.[28]

Risk assessment becomes even more challenging when it comes to trials involving investigational products that pose a 'higher level of uncertainty' than applies with conventional biomedical interventions.[29] The Presidential Commission for the Study of Bioethical Issues noted one of the biggest challenges in the oversight of synthetic biology as being 'its capacity to create novel entities that are increasingly dissimilar to known agents or organisms, making potential risks harder to assess'.[30] A further impediment is the potential length of time before a risk eventuates. Here, it is useful to differentiate more traditional drug treatments, which tend to be metabolised and their by-products eliminated within a limited time-period. This largely confines the risk of adverse events.[31] No such constraints apply with synthetic biology and most other highly innovative experimental products. Lessons here can be drawn from reports in 2014 of a research participant who developed a spinal cord mass eight years after an early-phase experimental stem cell transplantation.[32] Notably, the published clinical trial report for this study pronounced the procedure as

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21 Stuart H Orkin and Arno G Motulsky, 'Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy' 2 <osp.od.nih.gov/sites/default/files/resources/Orkin_Motulsky_Report.pdf>.

22 Ibid 1.

23 N E Kass et al, 'Balancing Justice and Autonomy in Clinical Research With Healthy Volunteers' (2007) 82 *Clinical Pharmacology & Therapeutics* 219.

24 M Sibille et al, 'Adverse Events in Phase-I Studies: A Report in 1015 Healthy Volunteers' (1998) 54 *European Journal of Clinical Pharmacology* 13; M Orme et al, 'Healthy Volunteer Studies in Great Britain: The Results of a Survey into 12 Months Activity in This Field' (1989) 27 *British Journal of Clinical Pharmacology* 125.

25 J Savulescu, 'Two Deaths and Two Lessons: Is It Time to Review the Structure and Function of Research Ethics Committees?' (2002) 28 *Journal of Medical Ethics* 1.

26 Peter Mitchell, 'Critics Pan Timid European Response to TeGenero Disaster' (2007) 25 *Nature Biotechnology* 485; Ezekiel J Emanuel and Franklin G Miller, 'Money and Distorted Ethical Judgments about Research: Ethical Assessment of the TeGenero TGN1412 Trial' (2007) 7 *The American Journal of Bioethics* 76.

27 Cormac Sheridan, 'TeGenero Fiasco Prompts Regulatory Rethink' (2006) 24 *Nature Biotechnology* 475.

28 Tony Tse, Rebecca J Williams and Deborah A Zarin, 'Reporting "Basic Results" in ClinicalTrials.gov' (2009) 136 *Chest* 295.

29 Rebecca Dresser, 'Building an Ethical Foundation for First-in-Human Nanotrials' (2012) 40 *The Journal of Law, Medicine & Ethics* 802, 802.

30 The Presidential Commission for the Study of Bioethical Issues, above n 1, 83.

31 Pascale G Hess, 'Risk of Tumorigenesis in First-in-Human Trials of Embryonic Stem Cell Neural Derivatives: Ethics in the Face of Long-Term Uncertainty' (2009) 16 *Accountability in Research* 175, 183.

32 Brian J Dlouhy et al, 'Autograft-Derived Spinal Cord Mass Following Olfactory Mucosal Cell Transplantation in a Spinal Cord Injury Patient' (2014) 21 *Journal of Neurosurgery: Spine* 618.

'feasible, relatively safe, and potentially beneficial' based on a follow-up period of up to 42 months.[33]

B *Normative Nature of Risk-Benefit Assessments*

Risk is often conceptualised as a technical formulation, capable of precise measurement and weighing. Yet estimates of the magnitude of risk also are context-dependent and require moral and social judgments. In other words, we make normative judgments about the magnitude of respective harms and benefits, should they occur, as well as how much value the research data would have for society at large.[34] Members of the public (lay persons), for example, have been shown to perceive risk as higher whenever 'potential harms are dreaded, unobservable, or have delayed manifestations'.[35] People also tend to perceive common and unspectacular events, such as asthma and stroke, as less risky than they really are.[36] Additionally, the more an activity is thought to yield large benefits, the lower its risks are perceived to be. Persons who hold a high opinion about the benefits of a given technology (often scientists in the field) are therefore likely to regard research risks as lower than those without such an opinion (often lay persons).[37] This has clear implications for the constitution of any oversight body.

C *No Agreed Framework for Assessing the Acceptability of a Risk Level*

Risk assessments are complicated further by the lack of a commonly agreed risk framework for assessing and weighing study risks and benefits. Two schools of thought on weighing trial risks have gained traction but neither provides ready answers on the acceptability of a given risk level for non-therapeutic trial interventions. The component analysis test justifies the risks of therapeutic interventions based on a participant's clinical interests: that is, whether the intervention is in 'clinical equipoise'.[38] For non-therapeutic interventions — which will include most, if not all, early phase trials[39] — risks must be minimised to the greatest extent possible and be reasonable in relation to the knowledge the study may generate. In comparison, the net risks test evaluates all research interventions based on the principle of non-exploitation: that research participants are not exposed to excessive risks of harm for the benefit of others.[40] However, neither of these tests specifies a substantive standard for acceptable levels of research risks,[41] in relation to potential benefits of research.[42] Determining what is a 'reasonable' or 'not excessive' risk therefore becomes an essentially

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33 Carlos Lima et al, 'Olfactory Mucosa Autografts in Human Spinal Cord Injury: A Pilot Clinical Study' (2006) 29 *Journal of Spinal Cord Medicine* 191.

34 Annette Rid, 'Risk and Risk-Benefit Evaluations in Biomedical Research' in Sabine Roeser et al (eds), *Handbook of Risk Theory: Epistemology, Decision Theory, Ethics, and Social Implications of Risk* (Springer Science & Business Media, 2011) 180, 184.

35 Jonathan Kimmelman, 'Valuing Risk: The Ethical Review of Clinical Trial Safety' (2004) 14 *Kennedy Institute of Ethics Journal* 369, 377.

36 Paul Slovic, Baruch Fischhoff and Sarah Lichtenstein, 'Facts and Fears: Understanding Perceived Risk' in Richard C Schwing and Walter A Albers (eds), *Societal Risk Assessment* (Springer Science & Business Media, 1980) 181.

37 Kimmelman, above n 35, 377.

38 Benjamin Freedman, 'Equipoise and the Ethics of Clinical Research' (1987) 317 *New England Journal of Medicine* 141.

39 James A Anderson and Jonathan Kimmelman, 'Extending Clinical Equipoise to Phase 1 Trials Involving Patients: Unresolved Problems' (2010) 20 *Kennedy Institute of Ethics Journal* 75, 83.

40 For a more complete account of the non-exploitation framework, see: Franklin G Miller and Howard Brody, 'A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials' (2003) 33 *Hastings Center Report* 19; Franklin G Miller and Howard Brody, 'Clinical Equipoise and the Incoherence of Research Ethics' (2007) 32 *Journal of Medicine and Philosophy* 151.

41 In the context of component analysis, for non-therapeutic research risks.

42 Rid, above n 34, 199.

individual and intuitive judgment based on values that take into account other factors, such as the nature of potential benefits.[43]

In the absence of ready substantive answers, some commentators have proposed reliance on procedural solutions for ascertaining the acceptability of trial risks. Rid and Wendler suggest that those reviewing the acceptable upper limit of trial risks should ask whether an 'informed and impartial social arbiter' would recommend the trial based on a comparison of trial interventions with other activities involving an equivalent risk level, and a weighing of those risks against the value of the trial information.[44] For example, the risk of a serious haemorrhage from a liver biopsy could be compared with the risk of serious injury from a charity soccer game.[45] The authors note, however, that as the net risks to participants increase, reasonable people are likely to disagree about risk-benefit judgments. This raises the need for an adequate process, including sufficient representativeness and transparency for the reviewing body to serve as 'legitimate arbiters of reasonable disagreement'.[46] The higher the cumulative net risks of a trial, the higher the requisite level of scrutiny and accountability is needed to perform this role.

V OVERSIGHT MECHANISMS IN AUSTRALIA

How then can Australia deal with the uncertainty and normativity of judgments about the acceptability of clinical trials with highly innovative experimental products, as would be the case with any future synthetic biology trials? Various regulatory strategies are in place, but — at least as presently operating — none of these are sufficient to satisfy the trifold challenges of risk-benefit assessments for highly innovative clinical trials.

A *Office of the Gene Technology Regulator*

The Office of the Gene Technology Regulator ('OGTR') is a Commonwealth Government regulator responsible for reviewing product dealings that contain genetically modified organisms. To fall within the OGTR's scope, as defined in s 10 of the *Gene Technology Act 2000* (Cth) ('*Gene Technology Act*'), an investigational product must be a live organism that has been modified by gene technology or has inherited modified traits. The product must be capable of reproduction or of transferring genetic material.

Product dealings that fall within the scope of OGTR's review are subject to a systematic scientific risk assessment process through the preparation of a Risk Assessment and Risk Management Plan. This plan identifies any risks to human health and safety and to the environment that the product dealing would pose. The required procedures for developing this plan differ depending on whether the release of the genetically modified product into the environment is intentional or unintentional. For intentional releases,[47] the Regulator must seek input from the Gene Technology Technical Advisory Committee ('GTTAC'), comprised of experts in relevant scientific fields including stem cell therapy, molecular biology, immunology, and plant science. The Regulator also must seek comment on the risk management plan from the States and Territories, prescribed Commonwealth authorities,

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43 Institute of Medicine (US) et al, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* (2014) 26 <http://www.ncbi.nlm.nih.gov/books/NBK174837/>.

44 Annette Rid and David Wendler, 'A Framework for Risk-Benefit Evaluations in Biomedical Research' (2011) 21 *Kennedy Institute of Ethics Journal* 141.

45 Ibid 166.

46 Ibid 167.

47 Under s 11 of the *Gene Technology Act 2000* (Cth), an intentional occurs if the GMO is 'intentionally released into the open environment, whether or not it is released with provision for limiting the dissemination or persistence of the GMO or its genetic material in the environment'.

local councils, and the public.[48] For unintentional releases (which relates to products that are not intentionally released into the open environment and has included the vast majority of clinical trial products),[49] the Regulator is permitted, but not required, to consult such persons and bodies.[50] Notably, the legislation does not provide for the Regulator to consult with members of the public on licences for unintentional releases.

To date, Phase III clinical trials of a genetically modified cholera vaccine provide the only example of a review of an 'intentional release' of a genetically modified clinical trial product under the *Gene Technology Act*.[51] The OGTR adopted a relatively constrained role, expressly deferring to the Therapeutic Goods Administration ('TGA'), investigator, sponsor, and role of Human Research Ethics Committees ('HREC') in ensuring participant safety. The Regulator explained that:

> In order to avoid duplication of regulatory oversight, as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment.[52]

The OGTR approved the application contingent on a range of risk mitigation procedures.[53] A number of licences have been issued for clinical trial products defined as unintentional releases;[54] however, the limited information publicly available precludes a deeper analysis of the approval process.

The OGTR is well placed to meet most of the challenges that beset risk-benefit assessments for highly innovative investigational products, especially when intentional product release procedures are followed. The OGTR has access to excellent expertise — especially through the GTTAC — so it should have the capacity to make an assessment of scientifically complex benefits and risks.[55] At least for intentional releases, the Regulator's processes also address the normative nature of risk assessments through the requirement for broad expert and public consultation. A 2011 review of the *Gene Technology Act* praised the OGTR's extensive communication strategies, including advertising individual protocols in high-profile state

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48 *Gene Technology Act 2000* (Cth) s 52.

49 For example, DNIR-536, 'Clinical study if the efficacy and safety of intrra-tumoural injection of genetically modified ASN-002 in nodular basal cell carcinoma in a clinical study'; DNIR-523, 'A clinical trial to treat Hemophilia B using AAV-based gene therapy'; DNIR-501, 'A phase 1 study of autologous GD2 chimeric antigen receptor-expressing peripheral blood T cells in patients with metastatic melanoma': Office of the Gene Technology Regulator, *List of Applications and Licences for Dealings Not Involving an Intentional Release (DNIR) of a GMO into the Environment* <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/contained-1>.

50 *Gene Technology Act 2000* (Cth) s 47.

51 Office of the Gene Technology Regulator, *Issue of Licence DIR 126 to PaxVax Australia Pty Ltd for a Clinical Trial of a Genetically Modified Vaccine against Cholera* (10 April 2014) <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir126notific-htm>. The vaccine is excreted from participants into sewage and waste water, thereby constituting a release into the open environment.

52 Office of the Gene Technology Regulator, 'Risk Assessment and Risk Management Plan for DIR 126: Clinical Trial of a Genetically Modified Vaccine against Cholera' 9 <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/65A3E9592160CA92CA257C1F007F38BA/$File/dir126rarmp.pdf>.

53 Ibid 39.

54 For example, DNIR-536, 'Clinical study if the efficacy and safety of intrra-tumoural injection of genetically modified ASN-002 in nodular basal cell carcinoma in a clinical study'; DNIR-523, 'A clinical trial to treat Hemophilia B using AAV-based gene therapy'; DNIR-501, 'A phase 1 study of autologous GD2 chimeric antigen receptor-expressing peripheral blood T cells in patients with metastatic melanoma': Office of the Gene Technology Regulator, *List of Applications and Licences for Dealings Not Involving an Intentional Release (DNIR) of a GMO into the Environment* <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/contained-1>.

55 The Allen Consulting Group, 'Review of the Gene Technology Act 2000' (August 2011) <http://www.health.gov.au/internet/main/publishing.nsf/Content/gene-techact-review> advised that the GTTAC 'appears to be working very well'.

and national newspapers and circulating advice to an email list of approximately 700 interested stakeholders.[56] Dedicated advice by the Gene Technology Ethics and Community Consultative Committee enhances the consultative process,[57] which is an important addition given theoretical and practical concerns about the efficacy of public engagement in technical decision making and risk assessment.[58] Finally, when reviewing intentional releases, the OGTR appears to satisfy Rid and Wendler's conditions for an 'ideal social arbiter'.[59] Evaluations are based on formalised risk assessment processes with input from a variety of government offices along with an expert scientific committee. The review process also allows for extensive public scrutiny and input.

Despite its clear benefits, full OGTR review only applies to a few highly innovative investigational products. For one, the definition of products that fall within the Regulator's scope is highly specific,[60] raising questions about its comprehensiveness for current and future synthetic biology products. The definition also excludes other kinds of highly innovative investigational products, such as nanotechnology. Moreover, many of the regulatory processes crucial for satisfying the conditions for optimal risk-benefit assessments (public consultation, mandatory expert scientific consultation, public availability of licensing information) apply only to an intentional product release, which omits the majority of early-phase trials. Finally, in the one instance in which the OGTR has reviewed the intentional release of a clinical trial product, it refrained from assessing the risks and benefits for individual participants. These were expressly deferred to the TGA and reviewing the HRECs. Everything else being equal, avoiding duplicative regulatory oversight is a worthy goal. However, this strategy warrants reassessment in light of the limited capacity for the TGA and HRECs to address the trifold challenges of reviewing the risks and benefits of synthetic biology and other highly innovative investigational products.

B *Therapeutic Goods Administration*

The TGA is a Commonwealth statutory authority responsible for therapeutic goods in Australia. Before any investigational product can be used in clinical trials, the trial sponsor must satisfy the requirements of either the Clinical Trial Notification ('CTN') Scheme or the Clinical Trial Exemption ('CTX') Scheme. These pathways involve very different levels of TGA review and oversight.

The TGA plays a limited review role under the CTN Scheme. An HREC is responsible for reviewing all data relating to the clinical trial, including its scientific validity and ethical acceptability. After HREC approval, the CTN form is sent to the TGA to notify it of the trial. The TGA plays a more active role in evaluating proposed clinical trials under the CTX scheme. Under this scheme, the trial sponsor must lodge an application to conduct clinical trials with the TGA. A TGA delegate is then made responsible for reviewing product information, including any preclinical and clinical data. If no objection is raised, the trials may proceed.[61] The TGA has the discretion during the review process to seek input from relevant advisory committees, predominantly comprised of scientific subject-matter experts. In the synthetic biology context, this would most likely fall to the Advisory Committee on Biologicals.[62]

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56 Ibid 33.
57 *Gene Technology Act 2000* (Cth) s 107.
58 Sherry Arnstein, 'A Ladder Of Citizen Participation' (1969) 35 *Journal of the American Planning Association* 216; John Gaventa and Andrea Cornwall, 'Power and Knowledge' in Peter Reason (ed), *Handbook of Action Research: Participative Inquiry and Practice* (SAGE, 2001) 70.
59 Rid and Wendler, above n 44.
60 *Gene Technology Act 2000* (Cth) s 10.
61 Therapeutic Goods Administration, *Clinical Trials at a Glance* (18 May 2001) <https://www.tga.gov.au/clinical-trials-glance>.
62 Established under the *Therapeutic Goods Regulations 1990* (Cth), pt 6 div 1EA.

The only investigational products for which the CTX scheme is mandatory are Class 4 biologicals. This is defined in the *Therapeutic Goods Act 1989* (Cth) as a product that 'comprises, contains or is derived from human cells or human tissues' that is processed using a method that goes beyond minimal manipulation and 'in a way that changes an inherent biochemical, physiological or immunological property'.[63] Under the *Therapeutic Goods (Things that are not Biologicals) Determination* of 2011 other products are specified as not constituting biologicals, including recombinant DNA products.[64] A product also can be declared in the regulations as a Class 4 biological.[65]

Except in these quite limited circumstances, a trial sponsor can choose whether to use CTN or CTX. The TGA advises that 'as a general rule', later-phase studies are most suited to the CTN scheme, and the CTX scheme may be 'more appropriate where the experimental device introduces new technology, new material or a new treatment concept which has not been evaluated previously in clinical trials in any country'.[66] An HREC that receives an application to review a trial under the CTN scheme may advise that it has insufficient expertise and recommend the trial's review under the CTX scheme, although it appears that such a course of action is relatively unusual. A 2005 review of access to unapproved therapeutic goods in Australia reported that, in 2000 (the most recent year for which data was available), only two clinical trials went through the CTX scheme. This is compared to the 589 trials that went through the CTN scheme during the same period.[67] This included most Phase I and II trials.[68] It is impossible from the available data to extrapolate the likelihood of a highly innovative investigational product going through the CTX scheme. Tellingly, however, the Report advised of HRECs' 'overwhelming willingness' to conduct substantial scientific reviews rather than refer trials back through the CTX process.[69]

In sum, the TGA regulatory framework is less suitable to meet the challenges of risk-benefit assessments for highly innovative investigational products than the OGTR. The TGA has the capacity to conduct a rigorous scientific analysis of relevant risks and benefits, particularly where the Administration receives input from a relevant advisory committee. However, the process has no clear avenue for addressing the normative aspects of risk-benefit assessments. TGA reviews are confidential and are not open to public input or submissions. The expertise available to the TGA through advisory committees is technical in nature, which limits its scope for reflection on public perceptions of risk and benefit. The TGA process also satisfies fewer of the criteria for an ideal social arbiter than the OGTR, lessening its potential to address the lack of substantive standards for judging the acceptability of risk-benefit assessments. In many circumstances, a TGA officer alone can make a CTX decision. Review by expert advisory committees is discretionary and technology-specific. Neither the TGA nor the relevant advisory committees have in place processes to make risk assessments (and the principles on which they are founded) publicly accessible, precluding the requisite level of transparency and accountability.[70] Moreover, in practice, only a select few investigational products will receive any TGA scrutiny of product information. Only those products that meet the complex definition of a Class 4 Biological are required to go through the CTX

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63 *Therapeutic Goods Act 1989* (Cth) s 32A. See also Therapeutic Goods Administration, *Australian Regulatory Guidelines for Biologicals: Part 1* <http://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb>.

64 Secretary of the Department of Health and Ageing, *Therapeutic Goods (Things that are not Biologicals) Determination 2011,* No 1, 31 May 2011, s 3(e)(ii).

65 At the time of writing, no biological was so declared.

66 Therapeutic Goods Administration, *Access to Unapproved Therapeutic Goods — Clinical Trials in Australia,* 14–15 <http://www.tga.gov.au/publication/access-unapproved-therapeutic-goods-clinical-trials-australia>.

67 Banscott Health Consulting, *Report of the Review of Access to Unapproved Therapeutic Goods*, 38.

68 Ibid 66.

69 Ibid 71.

70 Some information may be discoverable under freedom of information laws; however, this cannot equate to proactive publication in the context of satisfying conditions for an 'ideal social arbiter'.

Scheme. While sponsors may choose to use the CTX scheme, or a reviewing HREC may refer such trials, available data shows the rarity of these actions.

C *Human Research Ethics Committees*

Receipt of National Health and Medical Research Council ('NHMRC') funding is preconditioned on a research institute's compliance with the National Statement, including its requirement for an HREC to review the ethical acceptability of all research involving humans. This makes HRECs the bodies with the most broad-ranging and consistent oversight of clinical trials, including early-phase clinical trials. For trials going through the CTN scheme, an HREC may be the only review of the risk-benefit calculus for individual participants.[71] Even where the TGA has reviewed an experimental product under the CTX scheme, HRECs still have sole responsibility for reviewing individual trial protocols.[72]

Almost all Australian HRECs are established by individual research institutions,[73] which are responsible for ensuring that the Committee is adequately resourced and maintained,[74] and have procedures that promote 'good ethical review'.[75] To fulfil National Statement criteria, HRECs also must satisfy certain membership criteria. They must comprise a roughly equal gender balance, at least one-third of the members being from outside the institution, and membership of laypersons, persons with expertise in professional care or counselling, a person who performs a pastoral care role, a lawyer, and persons with research experience.[76] Moreover, 'wherever possible one or more of the members ... should be experienced in reflecting on and analysing ethical decision-making'.[77]

The National Statement sets out four broad values and principles on which HRECs make decisions about a trial's ethical acceptability: research merit and integrity, justice, beneficence, and respect for those involved in research. Specific rules further delineate these values and principles: most relevantly, that the value of beneficence requires an assessment of the risks of harm to research participants and others. The National Statement advises that 'risks to research participants are ethically acceptable only if they are justified by the potential benefits of the research'.[78] It goes on to note that

> in determining the existence, likelihood and severity of risks, [HRECs] should base their assessments on the available evidence ... [and] consider whether to seek advice from others who have experience with the same methodology, population, and research domain.[79]

The manner in which HRECs determine whether these National Statement criteria have been satisfied varies widely, and is subject to limited transparency and oversight. To maintain their accreditation status, each HREC must file an annual report with the NHMRC advising of their composition, processes for assessing research proposals, reporting

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71 Where products involve genetic manipulation, review by an Institutional Biosafety Committee ('IBC') also will be required. IBCs provide institutions with advice on the identification and management of risks associated with GMO dealings, including GMO containment: Office of the Gene Technology Regulator, 'Explanatory Information on the Guidelines for Accreditation of Organisations' <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/accredguideinfo-Apr2013-toc/$FILE/accredguideinfo-Apr2013.pdf>.

72 Therapeutic Goods Administration, *Access to Unapproved Therapeutic Goods — Clinical Trials in Australia*, above n 66, 10–14.

73 A notable exception is the Bellberry HRECs, which have been established by a private not-for-profit company: Bellberry Limited, *Welcome to Bellberry Limited* <http://www.bellberry.com.au/>.

74 Australian Government National Health and Medical Research Council, above n 9, 5.1.26.

75 Ibid 5.1.37.

76 Ibid 5.1.30.

77 Ibid 5.1.32.

78 Ibid 2.1.2.

79 Ibid 2.1.4.

arrangements, complaint handling, and processes for monitoring of approved research. However, this process relies almost exclusively on self-reporting. As Susan Dodds has noted, '[w]hile it is certain that HRECs strive to meet the requirements of the National Statement, if an HREC is not aware that its processes are inadequate, it is not going to report its lack of compliance in the annual report'.[80] Many HRECs are now subject to additional accountability based on their status as a Certified Reviewing HREC under the national Mutual Acceptance Scheme for single ethical and scientific review of multi-centre research.[81] Certification requires assessment by the NHMRC of the HREC's review processes including an on-site visit from an assessment team. HRECs are certified for specific research categories, including various phases of clinical trials (Phases 0, I, II, III, and IV).[82]

This raises the question of how well HRECs are placed to satisfy the challenges of risk-benefit assessments for highly innovative experimental products. The first challenge is grappling with the uncertain nature of risks associated with highly innovative clinical trials. Since HRECs differ widely in their processes and the scientific expertise they have available to them, sweeping statements are unwise in this regard. However, the task is formidable. An HREC reviewing an early phase trial must locate expertise in disciplines as broad as clinical pharmacology, toxicology, trial design and methodology, in addition to the area of specialty of the particular trial. Yet this responsibility is imposed without any transfer of resources, or even clear guidance about what constitutes a sufficient scientific review.[83] External experts are usually unpaid and uncompensated, with selection occurring in an uncontrolled and unevaluated way.[84] Given the identified challenges, there is reason to question HRECs' capacity to address the complex ratio of risks and benefits that characterise highly innovative experimental products.

Public transparency and accountability is a further issue with which HRECs struggle, limiting their potential to constitute 'ideal social arbiters' for the purpose of complex risk-benefit trade-offs. HREC meetings usually are treated as confidential,[85] as are meeting minutes.[86] While there are arguments to support such confidentiality, such as free and independent committee discussion and possible commercial implications, it also could be used to hide inadequacies in the reviewing process.[87] The confidential nature of HREC meetings also means that the general public is not able to access information about HREC workings and the reasoning for their decisions,[88] nor can members of the public contribute to these deliberations. This suggests an insufficient level of scrutiny and accountability to serve as 'legitimate arbiters of reasonable disagreement'.[89] Notably, Rid and Wendler use HRECs (in the US context in which they write, termed Institutional Review Boards ('IRBs'))

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80 Susan Dodds, 'Is the Australian HREC System Sustainable?' (2002) 21 *Monash Bioethics Review* 43.

81 National Health and Medical Research Council, *The National Approach to Single Ethical Review of Multi-Centre Research*, Human Research Ethics Portal <https://hrep.nhmrc.gov.au/national-approach>.

82 In the October 2014 list of institutions with certified ethical review processes, 10 of the 39 clinical trial certifications expressly covered Phase 0 trials: National Health and Medical Research Council, *List of Institutions with Certified Ethical Review Processes* <https://hrep.nhmrc.gov.au/certification/hrecs>.

83 Deborah Frew and Ainsley Martlew, 'Research Governance: New Hope for Ethics Committees?' (2007) 26 *Monash Bioethics Review* 17.

84 Savulescu, above n 25, 2.

85 Department of Health (NSW), *Standard Operating Procedures: Human Research Ethics Committees [GL2013_009]*, 21 <http://www.health.nsw.gov.au/ethics/Pages/re-and-g-policies.aspx>; Department of Health (Qld), *Standard Operating Procedures for Queensland Health HREC Administrators*, 42 <www.health.qld.gov.au/ohmr/documents/regu/hrec_sop.pdf>.

86 Department of Health (NSW), above n 85, 24; Department of Health (Qld), above n 85, 44.

87 Richard Ashcroft and Naomi Pfeffer, 'Ethics behind Closed Doors: Do Research Ethics Committees Need Secrecy?' (2001) 322 *British Medical Journal* 1294.

88 M Sheehan, 'Should Research Ethics Committees Meet in Public?' (2008) 34 *Journal of Medical Ethics* 631.

89 Rid and Wendler, above n 44, 167.

as an example of bodies that are insufficiently representative and transparent to evaluate studies involving high cumulative net risks.[90]

An area in which HRECs do have an advantage over bodies such as the TGA is their capacity to deal with the normative nature of risk benefit assessments. The National Statement sets out relatively broad membership requirements, including laypersons and persons who perform a pastoral care role in the community. A robust dialogue canvassing these varying perspectives would do much to forestall a purely technical characterisation of risks and benefits. Yet this presupposes the meaningful participation of all members in discussions of the risk-benefit calculus, which there are reasons to doubt. In a 1994 publication that assessed HREC members' decision-making influence, both administrators and medical graduates were rated as significantly more active and important than the remaining members, including lawyers, ministers of religion and lay members.[91] The authors noted that 'the finding raises the question whether lay members can effectively balance any bias that medical, scientific, and other institutional members may bring to the committee'.[92] These findings are consistent with more recent empirical research in the US, reporting that lay members feel they lack influence as compared with scientific members.[93]

VI DISCUSSION

The preceding discussion has highlighted the difficulties that face Australia's present regulatory bodies when assessing the risks and benefits of highly innovative investigational products, such as those likely to emerge through synthetic biology. While the OGTR is best equipped to deal with these multifold challenges, the Regulator has so far taken a relatively hands-off approach to clinical trial products, due to these products' usual classification as an 'unintentional release', as well as concerns about duplicating the oversight functions of the TGA and HRECs. Several options for reform are available, including expanding the scope of OGTR reviews of investigational products, requiring TGA review of investigational products that meet predefined risk criteria, and establishing more specialised HRECs to review early-phase clinical trials involving highly innovative products.

A *Expanding and Integrating OGTR Review*

Given the benefits of the OGTR review procedure for satisfying the multifold challenges of complex risk-benefit assessments, consideration is warranted of extending its remit to cover a broader spectrum of clinical trials with highly innovative investigational products. The main proviso is whether this can be achieved in a practical manner and without unduly duplicating regulatory activities.

Experience from the US Recombinant DNA Advisory Committee ('RAC') suggests at least the possibility of such an endeavour, along with some lessons for how it may be achieved. The RAC has considerable similarities to the OGTR, including a purview of the scientific and ethical acceptability of novel gene therapy research protocols and scope for public participation in reviews.[94] The model has been credited with easing public fears about the safety and appropriateness of gene transfer research,[95] and generating specialist institutional

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90 Ibid.

91 Paul M McNeill, Catherine A Berglund and Ian W Webster, 'How Much Influence Do Various Members Have within Research Ethics Committees?' (1994) 3 *Cambridge Quarterly of Healthcare Ethics* 522.

92 Ibid 526.

93 Sohini Sengupta and Bernard Lo, 'The Roles and Experiences of Nonaffiliated and Non-Scientist Members of Institutional Review Boards' (2003) 78 *Academic Medicine: Journal of the Association of American Medical Colleges* 212.

94 Institute of Medicine (US) et al, above n 43, 47.

95 Joseph M Rainsbury, 'Biotechnology on the RAC - FDA/NIH Regulation of Human Gene Therapy' (2000) 55 *Food and Drug Law Journal* 575, 598–9; Institute of Medicine (US) et al, above n 43, 49.

knowledge about recurring gene transfer issues.[96] The Institute of Medicine ('IOM') has recently assessed the model as providing ongoing benefits that warrant its retention in the IOM Report.[97]

The procedures followed by the RAC have changed considerably since its inception to maximise its utility for the Food and Drug Administration ('FDA') and ethics committees (IRBs in the US) and to minimise undue regulatory burden. For one, RAC review has been restricted to those applications deemed as being particularly risky. Originally the RAC reviewed and approved all gene transfer research at institutions receiving related NIH research funds. As the amount of research accelerated and certain kinds of procedures became more mainstream, reviews were limited to novel protocols that presented specific safety or ethical issues, thereby ensuring that duplication is limited to those clinical trials for which robust oversight is most needed.[98] Reviews now are initiated by recommendations from at least three RAC members or the NIH director regarding the novelty of the research and the level of risk it poses to participants.[99] As a result, only about 20 per cent of protocols submitted to the RAC are selected for additional review.[100] The IOM Report recommended further limiting RAC review to trials that satisfy the following criteria, as identified by the Office of the Director of the NIH:

1. Protocol review could not be adequately performed by other regulatory and oversight processes (for example, institutional review boards, institutional biosafety committees, the US Food and Drug Administration);
2. One or more of the criteria below are satisfied:
    - The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.
    - The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.
    - The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.[101]

Constraining OGTR clinical trial reviews in a similar way could ensure that the regulatory burden is focused on those product dealings that raise the greatest need for expert and transparent risk-benefit assessments – seemingly a far more targeted criterion than the current proxy of 'intentional' as compared with 'unintentional' releases.

The RAC review process also has been finessed to better integrate RAC findings with the more general regulatory processes for clinical trials. Initially, IRBs gave gene therapy protocols a provisional approval and then deferred to the RAC before issuing a final approval.[102] In 2000, the timing of RAC reviews shifted to occur before, rather than after, IRB review, allowing IRBs to better incorporate into their review issues identified by the RAC.[103] The availability of such reviews has been credited with reassuring US ethics

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96 Nancy MP King, 'RAC Oversight of Gene Transfer Research: A Model Worth Extending?' (2002) 30 *The Journal of Law, Medicine & Ethics* 381, 383–4.
97 Institute of Medicine (US) et al, above n 43.
98 Ibid 46; Rainsbury, above n 95, 587–92.
99 Institute of Medicine (US) et al, above n 43, 51–2.
100 Ibid 16.
101 Institute of Medicine (US) et al, above n 43, Rec 4-1; The Director of the NIH accepted this recommendation: Francis S Collins, *Statement by the NIH Director on the IOM Report Addressing the Role of the Recombinant DNA Advisory Committee in Oversight of Clinical Gene Transfer Protocols* <http://www.nih.gov/about/director/05222014_statement_iom_rac.htm>.
102 Nelson A Wivel, 'Historical Perspectives Pertaining to the NIH Recombinant DNA Advisory Committee' (2014) 25 *Human Gene Therapy* 19, 21.
103 Institute of Medicine (US) et al, above n 43.

committee members that responsibility for entering into a new era of medicine did not rest solely on their shoulders.[104] The RAC findings also inform the various stages of review by the US drug regulator, the FDA.[105] Structuring OGTR review in this way would help to ensure that expanded OGTR oversight is most valuable for HRECs and the TGA, while minimising the regulatory burden placed on applicants.

A related question is whether the OGTR's mandate should be expanded beyond current legislative definitions of genetically modified products. While this would have the benefit of extending the benefits of a rigorous and publicly accountable review process to highly novel investigational products beyond technology-specific constraints, it raises some implementation challenges. In particular, the GTTAC is constituted on the basis of the expertise necessary to review gene transfer products.

Notably, the IOM Report recommended reforming the RAC to provide the capacity to review

> the full breadth of emerging areas of research supporting human clinical intervention that may have special risks and that could not be adequately assessed under the existing regulatory processes for clinical research.[106]

It suggested achieving this by either expanding the Committee's purview or by retaining a broad pool of subject matter experts who could be consulted on an ad hoc basis as issues or applications emerged.[107] Similar choices could be considered for the OGTR.

B *Improving the Assessment Available Through the TGA and HRECs*

In the absence of reforms identified above, OGTR review will not be an option for many highly innovative investigational products because they fall outside the realm of genetic modification (such as, nanotechnology products). Even within the realm of genetically modified products, most clinical trials will involve an 'unintentional' product release and therefore will receive an abbreviated OGTR review. Ensuring a favourable risk-benefit ratio for these products depends on HREC and TGA review. For the reasons explained earlier in this article, neither of these processes fully encapsulate the trifold challenges of assessing risks and benefits of highly innovative investigational products. In particular, neither review process satisfies the requisite level of transparency and public participation to constitute an 'ideal social arbiter' for the purposes of trading off risks and benefits. However, in combination, HREC and TGA reviews go a long way towards addressing the scientific complexities and normative judgments involved in such judgments.

Unfortunately, Australia's present clinical trial framework fails to ensure TGA review of highly innovative products. The only explicit requirement for review under the CTX scheme applies to Class 4 Biologicals. This depends on a complex, technical definition. While it captures many current synthetic biology applications, the definition's comprehensiveness requires dedicated attention, particularly to take into account future directions of the field. The definition is limited, for example, to products that comprise, contain or are derived from human cells or tissues. Would this cover, for example, a completely synthetic cell? Many other highly innovative investigational products will fall outside the definition's scope altogether. For these, scientific review is likely to remain the sole responsibility of reviewing HRECs. Yet a scientific review conducted by an HREC is 'likely to be a significantly different review than would have been conducted by TGA (or any other regulatory agency)'.[108] A

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[104] Rainsbury, above n 95, 598.
[105] Institute of Medicine (US) et al, above n 43, 55.
[106] Ibid 89.
[107] Ibid 92.
[108] Banscott Health Consulting, above n 67, 71.

technologically neutral, risk-based assessment is warranted for referring investigational products to the CTX scheme for a robust, standardised scientific assessment.

A possible framework in this regard can be drawn from the European Medicines Agency ('EMA') Guidelines on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products.[109] The Guidelines explain factors that increase the riskiness of experimental products, including the novelty of the mode of action, the extent of available knowledge about the product's target, and the relevance (or lack thereof) of animal species and models.[110] The EMA advises that:

> the higher the potential risk associated with an investigational medicinal product and its pharmacological target, the greater the precautionary measures that should be exercised in the design of the first-in-human study.[111]

In the Australian context, equivalent guidelines could indicate the need for review under the CTX scheme. This solution still falls short of the trifold challenges of assessing the risks and benefits of highly innovative investigational products as well as OGTR review — predominantly because of a lack of sufficient transparency and public engagement. However, at least the combination of HREC and TGA review ensures that the assessment of such products can address the scientific uncertainties of such risks and benefits and the normativity involved in weighing these risks and benefits.

A further option for facilitating a robust scientific assessment of highly innovative investigational products would be constituting a small number of specialist HRECs that would have sole authority for reviewing certain kinds of early-phase trials – termed by Julian Savulescu as 'suprainstitutional specialist committees'.[112] To some extent, this process has already begun through the NHMRC national certification scheme, under which some ethics committees have nominated themselves as having expertise in early phase trials. Arguably, however, reliance on specialist HRECs is less desirable for scientific review of highly innovative investigational products than referral for TGA review. At least for the foreseeable future, NHMRC certification is voluntary: there is no requirement that a certified committee review any given clinical trial. Nor are there clear guidelines or standards as to what constitutes sufficient expertise to undertake such review. More intractably, scientific review by any HREC lacks the imprimatur of Australia's therapeutic products regulator. A clear and accountable scientific assessment process is essential for promoting public trust in new, risky technologies. Whether a voluntary, institutionally dispersed ethics committee should ever be delegated complete responsibility for such a task is doubtful.

VII CONCLUSION

Harnessing the benefits of synthetic biology and other emerging technologies, while maintaining ethical protections for clinical trial participants, requires rigorous risk-benefit assessments. Such assessments face multifold challenges: most notably, the inherent complexity of ascertaining likely risks and benefits, the normativity underpinning how those risks and benefits are weighed, and the lack of ready substantive standards for determining any acceptable level of risks to which participants could ethically be exposed. Australia's present regulatory framework is insufficiently equipped to address the challenges of risk-benefit assessments for clinical trials involving highly innovative investigational products. The OGTR provides the most promising processes in this regard, including access to high-quality scientific expertise, avenues to engage a broad spectrum of perspectives in regulatory

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109 European Medicines Agency, above n 12.
110 Ibid 4.1.
111 Ibid 4.4.1.
112 Savulescu, above n 25, 2.

decision-making, including members of the public, and transparent and accountable procedures. However, such review procedures apply to a very limited number of clinical trials, limited by technical definitions that lack a ready focus on targeting the most risky dealings. Responsibility for the overwhelming majority of risk-benefit assessments for clinical trials involving highly innovative investigational products falls to the TGA and individual HRECs. Unfortunately, both of these review processes face clear gaps in their capacity to meet the challenges of undertaking risk-benefit assessments in this context. Regulatory reforms focused on expanding the OGTR's remit, along with strengthening HREC and TGA review requirements, will place Australia in a good position for assessing future advances.

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