

Cambridge University Press

978-0-521-69084-3 - Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation

Jonathan Kimmelman

Index

[More information](#)

Index

- a priori* power calculations 119
- Abiocr 181
- accelerated titration design 77
- ACTG 076 regimen 135
- action bias 186
- ADA-SCID 132, 162
- ADA-SCID study (Milan group) 105, 132–3, 139, 140, 164, 188
- attractiveness for gene transfer 132
- PEG-ADA availability and costs 132
- results 132–3
- adeno-associated virus (AAV) vectors 12, 37
- in brains of non-terminal patients 110
- GAD gene transfer in Parkinson's disease 110
- hemophilia study 92, 93, 163
- immune response to 92, 93
- insertion near actively transcribed genes 163
- preclinical and phase 1 study findings 92
- reference standard 63
- response to in dogs vs. humans 92
- serotypes 12
- toxicity 52
- adenosine deaminase deficient SCID, study *see* ADA-SCID study
- adenoviruses as vectors 11
 - adverse event reporting, low rate 38
 - hepatic toxicity 39
 - immune reactions to 32, 54
 - OTC.019 (Gelsinger) study 31–2 *see also* OTCD study
 - reference standard 63
 - risk minimization strategies 57
 - third generation 57, 122
 - toxicity in OTCD study *see* OTCD study
 - toxicity in rabbits 39
 - toxicity in rhesus monkeys 34
- advance purchase agreements 145, 147
 - with discriminatory pricing 147
- adverse events
 - delayed, detection mechanisms 64–5
 - long-term follow-up 59, 64–5
 - costs vs value 65
 - reporting 59
 - low rate, adenoviruses as vectors 38 *see also* OTCD study; X-SCID
- advocacy organizations 45
- age, exclusions from trials on basis of 91
- Agua, Nelson 178
- Aguirre, Gustavo 153
- Alliance for Eye and Vision Research 153
- American Cancer Society 94
- American College of Physicians 159
- American Society of Gene Therapy 16, 18, 26, 37, 42
 - recommendations for uncertainty reduction 66
 - retroviral gene transfer safety 59
- Anderson, W.F. 1, 24, 26, 112
 - first gene transfer trial, HTGS approval 156–7, 161, 162
 - OTCD study *see* OTCD study
- angiogenesis factors, for cell therapy 181
- angiogenesis inhibitors 160, 168
- animal models/data 54, 64
 - AAV-GAD gene transfer in Parkinson's disease 111, 126
- availability, scaling of evidentiary requirements 115–6
- bridging translational distance and 121
- cancer in companion animals 121
 - randomizing, preclinical evidence 119
 - supporting evidence, for gene transfer 111 *see also* preclinical studies/evidence
- anti-retrovirals
 - AZT, mother to child transmission prevention 135, 139
 - discriminatory pricing 146
- antisense agents 89
- arginase deficiency 8
- Ark Therapeutics 83
- aspirational benefits 74
 - benefits vs risks 75
 - evaluation 75–6
- Association of Health Care Journalists (AHCJ) 160
- attrition, in drug development 94
- augmerosen 89, 91
- Australia 22
- autopsies, information from 62, 65, 95
- Avigen 21, 133, 146
- AZT, mother to child transmission prevention 135, 139
- Baltimore, David 39
- bargaining model, for pre-trial agreements 138–9
- Batten disease 18
- Bayh-Dole Act 24, 123
- BCL-2 89
- Beck, Ulrich 179
- Belmont Report 134–5
- benefit–risk ratio 58
- benefits, of phase 1 trials *see* medical benefits for volunteers
- Bennett, Jean 153–4, 171
- “best risk estimate” 55

Index

- bias 186
 - action 186
 - confirmation 186
 - optimism, translational research and 123
 - in preclinical studies, reduced by blinding 119–20
 - publication 123
 - status quo 186
- biodistribution 13
- bioethics 20
- biomarkers 77
- biotechnology, decline in
 - support for gene transfer 14, 15
- Blaese, Michael 26, 156
- blinding, preclinical studies 119–20
- blindness, Leber’s congenital amaurosis preclinical studies 153
- bone marrow mononuclear cell injections 178, 180
- bone marrow transplantation 104, 165
- brain
 - AAV vectors in Parkinson’s disease *see* Parkinson’s disease
 - novel interventions for 182–3
- Brazil 23
- “bubble boy” disease
 - see* X-SCID (X-linked severe immune deficiency syndrome)
- Bush, Vannevar 24, 95
- bystander effect 99
- Canada 22, 25
- Canavan’s disease 73
- cancer
 - AAV vectors and 164
 - clinical equipoise of phase 1 studies 78–9
 - dosing strategies and design of studies 77
 - early-phase trials as medical opportunity 73
 - mortality, first gene transfer trial approval and 156–7
 - mouse xenograft model and 120–1
 - patients’ views on breakthroughs 168
 - phase 1 trials 18
 - therapeutic expectations 80–1
 - regulatory model for drug trials 94
 - targeted therapy 182
 - testicular, imatinib mesylate 74
- Cancer Therapy Evaluation Program (CTEP) 77, 94
- Caplan, Arthur 32, 38
- Casarett, David 103
- Cavazzana-Calvo, Marina 51, 60
- cell suicide 89, 99
- cell transfer/transplantation, stem cells *see* stem cell transfer
- Cerezyme 104
- Children’s Hospital of Philadelphia study 92
- China, gene transfer studies 23, 134, 141
- Cichon, Guenther 39
- CIOMS, preclinical evidence 113
- Cline, Martin 1, 122, 134
- clinical equipoise, concept 2, 78–9, 91, 112, 128, 184
 - advantages and problems 112
 - direct benefits of studies *vs* risk 78–9
- clinical trials
 - phases 15
 - volume decline 14, 15, 164, 166 *see also* phase 1 trials; phase 2 trials; phase 3 studies
- “close to the client” health systems 138
- coagulant factor 2, 92
 - costs 104, 140
 - neutralizing antibodies to 57 *see also* hemophilia and gene transfer
- Coartem 146
- coherence of arguments 185
- cohort-specific consent 77
- collateral benefits 74
 - ethical medical practice *vs* 75–6
 - evaluation 75–6
 - psychological benefits 74, 75, 76
 - risks compensated by 75
 - problems/objections to 75–6
- “collateral value” 93
- commercial pressures 61
- commercialization, of gene transfer 14, 17, 64
- companion animals, cancer intervention studies 121
- compassion for volunteers 72, 83
- complexity of studies, translational model of value 99
- confirmation bias 186
- conflicts of interest, financial *see* financial conflicts of interest
- consequences of proposals 185
- continual reassessment method 77
- Cooley, Denton 181
- Cooperative research and development agreement 211
- coronary disease, cell therapy 178, 181 *see also* Perin, Emerson
- coronary syndromes, acute 91
- cosmetic use, of gene therapy 9
- costs
 - coagulant factor 140
 - drugs for orphan disorders 140
 - gene transfer products 104, 188–9
 - humanitarian model of value and 104
 - limitation to translational model of value 100
 - PEG-ADA 132
- criminal activities 1
- Crystal, Ronald 1, 156
 - cystic fibrosis trial 158, 159, 161
- culture of safety 61
- Culver, Kenneth 133
- cystic fibrosis 13, 18
 - Crystal’s trial and protocol approval 158–9, 162
 - translational distance 118, 121
 - Trusts and Foundations for 18, 21
- cytokine cascade 31
- dacarbazine 89

Cambridge University Press

978-0-521-69084-3 - Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation

Jonathan Kimmelman

Index

[More information](#)

Index

- DARPA model 101–2
 data outliers 123
 data safety monitoring boards (DSMBs) 59, 60
 databases
 clinical trials 17
 gene transfer 14, 97
 incompletely analyzed data and 63
 tissue samples 66
 preclinical studies 124
 deception of public 160
 see also expectation management of gene transfer
 Decker, Donavon 161
 Declaration of Helsinki 90, 137
 2000
 revisions 135
 Defense Advanced Research Project Agency (DARPA) 101–2
 design of study *see* study design
 direct benefits (clinical improvement), of trials 74–5, 83
 evaluation 76–9
 argument from consistency with policy 79
 argument from data 76–7
 argument from design 77–8
 argument from equipoise 78–9
 reforms to improve, counterproductive 78
 risk–benefits 76
 surrogate benefits, distinguishing 82–3
 therapeutic vs nontherapeutic procedures 23, 74, 76
 disclosure policies 41
 deaths in 1999 trial 41
 discriminatory pricing 145, 146
 advance purchase agreements with 147
 leakage, concern over 146
 disease advocates 18, 45
 researcher relationship, expectation management 170
 disease foundations 18
 dogs, cancer rates, intervention studies 121
 dose
 accelerated titration design 77
 cancer trials 77
 escalation regimes 116
 functional vectors vs incomplete vector particles 62
 lack of standards 62–3
 starting, calculation 56
 subtherapeutic 77, 83
 dose-toxicity curves
 biphasic 32
 non-linear 31–2
 uncertainty and risk due to 55, 62
 drugs, new
 oncology, trials 3
 risky, regulatory evidence to rebut 143
 Duchenne’s muscular dystrophy 160
 During, Matthew 110
 early-phase trials
 inclusionism 72–3
 in LMICs *see* low-/middle-income countries (LMICs)
 as vehicle for care 73–4
 see also phase 1 trials
 enhancement gene transfer 23
 Entremed 160
 Environmental Protection Agency (EPA) 57
 enzyme replacement therapies 104
 epistemic orientation, of trials 90, 112
 equitable access licensing 145, 146
 Erickson, Robert 32
 Essential Medicines List (EML) 141
 ethicists 19–21
 ethics 19–20, 79
 oversight 21
 research *see* research ethics
 social purpose 21
 uncertainty shaped by 20–1
 ethics committees 100, 102
 ethics review bodies, caution over value assessments 106
 Europe, Road Map to 2010 25
 European Organization for Research and Treatment of Cancer 4
 European Society of Gene Therapy 16, 26
 Evans, John 20
 Evans, Rhys 51
 ex vivo delivery approach, gene transfer 13, 14
 expectation(s)
 as “network” phenomenon 156
 of public, management *see* expectation management of gene transfer
 therapeutic, of phase 1 trials *see* phase 1 trials
 translational research 154–5
 expectation management of cell therapy 181
 expectation management of gene transfer 5, 153–7, 185, 187
 adverse (Hard Times), management 155, 162–4
 appraising 164–7
 denial and defensiveness 163–4
 ethical consequences 169
 examples of trials 162
 historical precedent 163, 164–6, 169
 morale boosting 164
 reinterpreting disruptions 163
 X-SCID study 162
 asymmetries of
 communication 169
 building expectations 155
 complexity reduction, contingency 162
 consequences of
 mismanagement 167–9
 false hopes 168
 invalid-informed consent 167–8
 trust undermining 168, 169
 deficiencies in 166
 environment for 162
 ethical consequences 154–5
 ethical/optimal management 169–70, 185
 benefits 169
 concerns about instrumentalizing 169–70
 lack of 169

Cambridge University Press

978-0-521-69084-3 - Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation

Jonathan Kimmelman

Index

[More information](#)

Index

- expectation management of
 - gene transfer (*Cont.*)
 - recommendations 170–1
- Great Expectations (research promise projection) 155–8, 179
- Anderson and first gene transfer trial 156–7, 161
- appraising 159–2
- countering by researchers 170
- Crystal's cystic fibrosis trial 158–9, 162
- ethical consequences 168–9
- researchers responsible for 156
- Wilson and hypercholesterolemia trial 157–8, 160, 161
- medical sensationalism 160
- overselling (hype) 155, 156
- consequences 168–9
- as problem of information/truthful disclosures 159
- epistemological issue/no standards 160–1
- by researchers 154
- theatrical and nonverbal elements 154, 161
- recommendations 171
- transparency/equilibrium 170
- truthful disclosures interpretation 160
- experimental animals *see* animal models/data
- exploratory trials 116
- translational model of value 95
- external validity, translational distance and 120–1, 125
- AAV-GAD protocol 126
- Fair Benefits 137, 138–9
 - host communities free to negotiate 138
 - “how much”, not “what” 139
 - training/knowledge benefits 139 *see also* responsiveness, to host communities
- false hopes 168
- familial hypercholesterolemia trial (Wilson's) 157–8, 160, 161
- publication 162
- feasibility of policies 185
- fialuridine 32
- financial conflicts of interest 123, 124
 - OTCD study 35–6, 39
- Fischer, Alain 51
- Fletcher, Joseph 112
- Folkman, Judah 160
- Food and Drug Administration (FDA) 4, 56
 - accelerated approval process 73
 - adverse event reporting 59, 64
 - long-term follow-up costs 65
 - Critical Path initiative 25, 94
 - definition of phase 1 study 92
 - OTCD study 37–8
 - phase 1 study application review 79
 - pipeline problem 94
 - regulation of ooplasmic transfer studies 188
 - standards for supporting evidence 113
 - uncertainty reduction strategy, monitoring of volunteers 59
- Foundation Fighting Blindness 153, 171
- Foundation for Retina Research 171
- “407” studies 187
- Freedman, Benjamin 112
- French Anderson, W. *see* Anderson, W.F.
- Friedmann, Theodore 111, 125
- funding 24
 - difficulties, studies 16
 - sources 17 *see also* costs financial conflicts of interest
- Gaucher's disease 104, 140
- Gelsinger, Jesse 31, 32, 33, 36, 38, 55, 163
 - see also* OTCD study
- Gelsinger, Paul 32, 35, 36
- Gendicine 1, 141
- gene, definition 10
- gene addition 13
- gene marking 9
- gene replacement 13
- gene therapy 1, 9
- Gene Therapy Advisory Committee (UK) 64
- gene therapy policy conferences 59
- gene transfer 8–30
 - actors involved 15–21, 27
 - disease advocates 18
 - institutions 17
 - patients 18
 - regulators and ethicists 19–21
 - scientists 16–17
 - sponsors 17
- aims (therapeutic vs enhancement) 3–4, 23
- background to 8
- biological response, and failure 99–100
- condemnation of 156
- continuity with clinical medicine 2
- definition 9
 - deficiencies/complications of 9–10
- delivery approaches 13
 - ex vivo* 13, 14
 - in vivo* 13
- as distinct field 16
- as a drug?, differences 13–14
- as elastic evolving field 25
- ethical problems of translational research 4
- ethics, agenda 187–9
- genetic material 13
- geography 22–3
- indications/diseases included 23–4
- mixtures of genes 13, 62, 104
- as model for translational research 4–5
- nanotechnology with 183
- new phenomena and opportunities 27
- oversight/regulation *see* regulations for gene transfer
- pricing issues 104–5
- process 14–23
- product 9–14
- program 23–5
- research status and design faults, NIH panel 92–3

Cambridge University Press

978-0-521-69084-3 - Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation

Jonathan Kimmelman

Index

[More information](#)

Index

- resource-poor settings
 - see* low-middle-income countries (LMICs)
- stem cell transfer comparison 180–3
- strategies 11
- targets 10
 - foreign organisms 10
 - germ cells 10
 - somatic cells 10
- timeline 26
- vehicles and vectors 10–12, 179
 - mode of action 53
 - nonviral 11
 - regulated as biologics 21
 - risk minimization
 - strategies 57
 - viral *see* viral vectors
 - see also* gene transfer trials
- generic biologicals 20, 89
- gene transfer trials
 - benefit–risk ratio 58
 - decline in trial volume 165, 166
 - first trial 156–7
 - risk in *vs* drug trial risks 52
 - second trial (familial hypercholesterolemia) 157–8
 - stringent standard of value and 58
 - third trial (cystic fibrosis) 158–9 *see also* OTCD study;
 - Parkinson's disease;
 - X-SCID
- generic biologicals 20, 89
- genetic enhancement 3–4, 23
- ethics 188
- Genetic Technologies Inc. 24
- genetically modified viruses
 - immune response
 - modulation 9
 - see also* viral vectors
- Genasense® studies 100
- Genzyme Corp. 133, 146
- geography, of gene transfer 22–3
- germ cells, as gene transfer target 10, 187, 188
- Gleevec *see* imatinib mesylate (Gleevec)
- glioblastoma multiforme 72, 83
- Gliven International Patient Assistance Program (GIPAP) 145, 146
- glutamic acid decarboxylase (GAD), gene transfer 110
- Goffman, Erving 154
- growth hormone 53
- “halfway technology” 162
- Harkin, Senator 72
- Havrix 137
- health insurance 79
- Healy, Bernadine 72
- heart disease, cell therapy
 - 178, 181 *see also* Perin, Emerson
- hemophilia and gene transfer 2–4, 13, 23
 - AAV vector trial 92, 93, 163
 - animal models 115
 - Children's Hospital of Philadelphia study 92, 93
 - correspondence between preclinical/clinical studies 122
 - costs of clotting factors 104, 140
 - Essential Medicines List 141
 - as gene transfer model
 - benefits/advantages 2
 - limitations 2
 - Genzyme's pharmaco-philanthropy program 146
 - issues to consider for trials
 - 2–4
 - appropriate study population 3
 - evaluation of validity/value of trial 3
 - initiation of testing, timing 2–3
 - risk evaluation 3
 - risk evaluation (risks to others) 4
 - risks classification (to patients) 3–4
 - selection of patients 3, 57
 - in LMIC 133, 142
 - patient selection, risk minimization by 57
 - scientists involved 16
 - translational distance 118
- hepatitis A vaccine 137
- High, Katherine 163
- high-pay-off trials 101
- “high-reliability organizations” 60
- HIV 12, 54
 - mother to child transmission, AZT study 135, 139
 - vaccines 133
- HIV activism 73
- human embryonic stem cells (hES) 180
- Human Gene Therapy Subcommittee (HGTS) 156–7
- humanitarian model of value
 - 103–5, 184
 - applying 105–6
 - axes for assessing 103, 105
 - severity of unmet health need 103, 105
 - target population 103, 104
 - temporal 103, 104
 - threshold for 105
 - complexity of extending to translational trials 105
 - cost and access issues 104, 105, 188–9
 - gene transfer studies 104–5
 - translational model *vs* 103, 105 *see also* social value
- IL-10 (interleukin-10) 53
- imatinib mesylate (Gleevec) 74, 76, 77
 - GIPAP 145, 146
- immune-based toxicity 54–5
- immune response
 - to AAV vectors 92, 93
 - to adenovirus vectors 32, 54
 - OTCD study 31–2, 62
- immune response modulation, genetically modified viruses 9
- immunological status, measurement, standards 63
- inclusionism, early-phase trials 72–3
- indeterminacy 6
- informed consent 80–3
 - asking patients on motivations 83

Index

- informed consent (*Cont.*)
 - decisions shaped by expectations 155
 - invalid, consequence of expectation mismanagement 168
 - problems in OTCD study 36–7
 - telling patients clinical benefits unlikely 82
 - translational model of value and 95
 - validity, patient motivations for phase 1 trials 80
- initiation of human trials 2–3, 5, 110–31
 - cell therapy trials 181
 - clinical equipoise *see* clinical equipoise, concept
 - criteria, for GAD gene transfer 110
 - ethical justification of preclinical evidence 113–15
 - evidentiary standards
 - diminishing in terminal illness 117
 - novel agent trials 117–18
 - scaling by animal model availability 115–16
 - scaling by illness severity 117
 - scaling by risk 116–17, 127
 - formalized criteria 112–13
 - GAD gene transfer in Parkinson's disease 110–13
 - translational distance analysis 124–7
 - hunches and guesses inadequate 114, 115
 - procedural approach 113
 - shortcomings 113
 - risk–benefits 112
 - small-scale “exploratory” studies 116
 - strong supporting evidence for valuable trials 114–15
 - supporting evidence, threshold 118
 - translational distance *see* translational distance
- innate immunity, dose-toxicity and adenovirus vectors 31–2
- innovations
 - funding for 24
 - translational model of value, support for 95 *see also* novel interventions
- insertional mutagenesis 51
- Institutional Biosafety Committee (IBC) 22
- Institutional Review Board (IRB) 21, 44, 187
 - collateral benefits vs risks of trials 75
 - costs and access judgements 105
 - humanitarian model of value and 106
 - OTCD study 37–8
 - review of one trial protocol at once 102
- intellectual property licensing 146–7
- “intention to treat” 91
- internal consistency 185
- internal validity, translational distance and 119–20, 125
 - AAV-GAD protocol 126
- International Council on Harmonization 21
- Ioannidis, John 127
- Isner, Jeffrey 1
- “iterative value” 93
- Jewish Chronic Disease Hospital 137–8
- Jonas, Hans 75
- Jones, Stormie 157
- journals *see* publications, on gene transfer
- justice and translational trials 5, 134–6, 148
 - Kahneman, Daniel 186
 - Kaplett, Michael 110, 124, 167
 - Kay, Mark 163
 - Kelley, William 34, 36
 - Lancelot (dog) 153, 154, 171
 - Laski, Harold 161
 - law of small numbers 186
 - leakage, discriminatory pricing concern 146
 - Leber's congenital amaurosis (LCA) 153
 - human studies 171
 - preclinical studies 153, 171 *see also* Lancelot (dog)
 - Lenfant, Claude 158
 - lentiviruses as vectors 12
 - licenses 104
 - London, Alex 138
 - low-/middle-income countries (LMICs) 132–52
 - ADA-SCID trial 132–3
 - avoidable mortality 142
 - cell therapy trials 182
 - deployment of interventions 144
 - factors motivating early-phase trials 133–4, 142–3
 - expedience 133, 142, 143
 - fortuity 133, 142
 - operational advantages 133–4
 - prevalence of diseases 133
 - reasons for subject recruitment 133–4
 - ultra-rarity of diseases 133, 143
 - gene transfer agent benefits for 140–1
 - health care budgets 140–1
 - health needs as primary goal of studies 148
 - home-grown gene transfer programs 147–8
 - impediments to using gene interventions 141
 - justice and translational trials 134–6
 - medical skills/facilities limiting interventions 140
 - motivations for recruitment from 142–3
 - nonresponsive, studies being 147
 - post-trial access 137
 - responsiveness *see* responsiveness, to host communities

Index

- urgency of rare diseases 141
- lymphoproliferative disorders, in X-SCID trial *see* X-SCID
- Max Foundation 146
- McIvor, Scott 156
- MD Anderson Cancer Center 73
- measurement criteria, for proposals 185
- media
 - negative coverage of gene transfer studies 166–7
 - research publicity 154
 - Wilson’s familial hypercholesterolemia trial 162 *see also* expectation management of gene transfer
- medical benefits (of trials) for volunteers 5, 72–88
 - analysis and types 74–5
 - aspirational (scientific/medical) benefits *see* aspirational benefits
 - collateral (medical/non-medical) benefits *see* collateral benefits
 - direct benefits (clinical improvement) *see* direct benefits (clinical improvement)
 - justification of risk 79–80
 - phase 1 trials as medical opportunity 72–4
 - phase 1 trials as therapeutic *see* phase 1 trials
 - recommendations for assessment/disclosure 82
 - therapeutic ambiguity, motivation and informed consent 80–3
- Medical Research Council of India 159
- Medicare, U.S. 79
- melanoma, augmerosen study 89, 91
- meta-analyses 66, 77
 - planning for 66
- Milan ADA-SCID study *see* ADA-SCID study
- milestone payments 123
- Milstein, Alan 36
- Milto, P. and Milto, T. 18
- Minimal Anticipated Biological Effect Level (MABEL) 57
- missing data 123, 124
- mitochondria 10
- modest translational distance, principle 5, 118, 127, 128
 - AAV-GAD protocol 126
 - components and fulfilling 119
 - if animal models not available 121 *see also* translational distance
- Mohr, Jolee 37
- monitoring of volunteers 66
 - FDA and sponsors 59
 - risk and uncertainty minimization strategy 57
- Moorfields Eye Hospital 171
- morality, research in LMICs 134
- Motulsky, Arno 27, 92, 94, 115, 121, 163
- mouse xenograft model 120–1
- mucopolysaccharidosis type VII 133
- Mulligan, Richard 156
- muscular dystrophy 13, 160, 161
- Muscular Dystrophy Association 161
- nanomaterials 183
- nanotechnology 183
- National Bioethics Advisory Committee 139
- National Commission, Belmont Report 134–5
- National Gene Vector Laboratories (NGVL) 59, 63, 66
- National Hemophilia Foundation 21, 45
- National Institute of Cancer (NCI), funding 17
- National Institutes of Health (NIH) 4
 - budget and funding 24
 - database of gene transfer trials 97
- funding from, for gene transfer 17
- gene transfer, telling patients clinical benefits unlikely 82
- missed opportunities on vector safety 62
- Pioneer Award 101
- recommendations for uncertainty reduction 66
- Roadmap 4, 25, 101
- uncertainty minimization 59
- National Urea Cycles Disorder Foundation 33, 45
- “negative results”, of studies 99, 114, 115, 118, 183
- The Netherlands 22
- Nelkin, Dorothy 161
- no adverse effect level (NOAEL) 56
- non-novel agents, novel interventions vs, translational model of value 95–6, 113–14
- non-novel interventions 80
 - phase 1 testing 79, 113–14
- normalization of deviance 41
- normalization of risks 41–2
- Novartis
 - Coartem 146
 - GIPAP 145, 146
- novel interventions 79, 80, 113–14, 179
 - for brain 182–3
 - citations of phase 1 studies and 96
 - non-novel interventions vs 80, 95–6, 113–14
 - translational model of value and 95–6, 99, 113–14
 - value of information from studies on 96
- Nuremberg Code 90, 103, 113
- Ohio State University, muscular dystrophy study 161–2
- ooplasmic transfer 188
- opportunity cost, stringent value standard 58
- organization, of uncertainty/risk *see* uncertainty, and risk in gene transfer

Cambridge University Press

978-0-521-69084-3 - Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation

Jonathan Kimmelman

Index

[More information](#)

Index

- “organizational learning” 61, 62
 impediments 62–3, 64
 Orkin, Stuart 27, 92, 94, 115, 121, 163
 ornithine transcarbamylase deficiency (OTCD)
 see OTCD study
 orphan drugs 104, 133, 140, 188–9
 OTC.019 31
 OTCD study 14, 31
 death of patient (Gelsinger) 14, 31, 55, 62, 163
 lawsuit 32
 see also Gelsinger, Jesse
 risk/safety assessment
 acceptable risk, definition for 42–5
 adenoviral vectors and
 immune response 31–2, 62
 deviance toleration, risk
 normalization 41
 financial conflict of interest 35–6
 informed consent
 problems 36–7
 medically stable volunteer
 enrolled 32, 42
 nonlinear dose-toxicity
 curves 31–2
 normalizing risk 41–2
 personal ambition and
 misconduct 34–5
 protocol and dose-toxicity
 curves 32
 protocol violations 33–4
 risk classification challenge 39–41
 self-regulation lapse 38–9
 system/regulatory failures 37–8
 safety data integration across
 multiple trials after 62
 overselling, of technology 155, 156 *see also* expectation
 management of gene transfer
 oversight committees 42
 oversight/regulation 19, 21–2
 see also regulations for
 gene transfer

 Parkinson’s disease 53, 187

 GAD gene transfer 110, 162, 167
 acute vs chronic animal
 model 126
 adverse events in preclinical
 testing 124–5
 analysis 124–7
 correspondence of
 preclinical/clinical
 studies 126
 credibility of data 126
 criticisms 111, 126–7
 critics vs researchers 111
 external validity 126
 preclinical studies 126
 rescue strategy 111
 risks (administration/
 agent) 124–5
 support for 110
 translational distance 124
 primate model 111, 126
 patents 123
 patient advocates 44
 patients 18
 medically stable, in OTCD
 study 32–3
 motivation for trial *see* phase
 1 trials *see also* subject
 selection; *see* volunteers
 pediatric trials 187
 peer review, of press releases 170
 PEG-ADA 132
 Perin, Emerson 178, 180, 181, 184
 pharmaco-philanthropy
 program 145–6
 pharmacovigilance 66
 Phase 0 studies 25
 phase 1 trials 3, 14, 79
 cancer trials 18
 care vs research demarcation
 79, 81, 184
 definition, FDA 92
 direct benefits, policy and 79
 see also direct benefits
 (clinical
 improvement)
 heterogeneity of design 79
 inclusionism 72–3
 initiation *see* initiation of
 human trials
 lag between drug licensing
 and 104

 as medical opportunity for
 seriously ill patients
 72–4
 meta-analysis planning 66
 novel vs non-novel
 interventions 79, 113–14
 patient motivations for
 entering 80, 102
 asking, for informed
 consent 83
 for care 80
 progressive/sequential
 orientation 94
 purpose 5, 89–109
 efficacy assessment 89
 phase 2 trial planning
 89–90, 94
 social value *see* social
 value; value, of phase 1
 trial
 toxicity assessment 89
 recommendations for
 assessment/disclosure of
 benefit 82
 as “research procedure” 79,
 184
 success rates for advancing to
 phase 2 96, 97
 therapeutic expectations
 80–1, 83
 belief statements 80
 dampening by researchers
 81, 82
 frequency statements 80,
 81
 moral significance 81
 patient’s values/preferences
 affecting 81–2
 therapeutic justification 79
 ethical significance 80–1
 by patients 80
 therapeutic misconception
 reduction 81, 82
 asking patients on
 motivation 83
 clinical benefits unlikely,
 informing patients
 82
 clinical vs surrogate
 benefits 83
 practices interfering with
 therapeutic objective 83
 therapeutic objectives 77
 practices interfering 83

Index

- value of *see* value, of phase 1 trial
- as vehicle for care 73–4
see also early-phase trials
- phase 2 trials 3, 14
- planning, phase 1 trial role 89–90, 94
- success rate of phase 1 tests advancing to 96, 97
- phase 3 studies 90, 105, 179
- Piantadosi, Steven 94, 98
- pipeline problem 94
- population (for study) 3
 - hemophilia and gene transfer 3
 - humanitarian model of value 103, 104
- “positive result” 114
- positron emission tomography (PET) 75
- post-trial access 137, 184–5
- pox viruses, as vectors 12
- preclinical studies/evidence
 - AAV-GAD protocol 126
 - bias minimization 119–20
 - blindness, dogs 153, 171
see also Lancelot (dog)
 - correspondence with clinical studies 122
 - databases 124
 - death as endpoint 120
 - details of limitations/alternative explanations 123
 - ethical justification for trial initiation 113–15
 - evaluation 127
 - expectations based on 155
 - GAD gene transfer in Parkinson’s disease 111
 - hypothesis supported when alternative explanations refuted 114
 - methodological deficiencies 120
 - publication of 124
 - randomized animals 119
 - toxicological studies, publication 64
 - for translational trials 98
see also animal models/data
- press conference, familial hypercholesterolemia trial (Wilson’s) 157
- press releases, peer review 171
- pricing, gene transfer 104–5
- primates, Parkinson’s disease model 111, 126
- private foundations 18
- private sector, funding by 17
- professional misconduct 34–5
- Project Hope 146
- “proof of principle” studies 118
- proposals in book, agenda 185
- protocols for studies
 - centralized and transparent review 187
 - regulation/oversight 21
 - uncertainty reduction recommendations 64–5
 - violation in OTCD study (Gelsinger) 33–4
see also individual trials
- psychological benefits, of early phase trials 74, 75, 76
- publication bias 123
- publications, on gene transfer 14, 16
- lymphoproliferative disorder 60
- nonpublication issues 77, 123
 - organizational learning reduction 64
 - rates for phase 1 studies 97
- preclinical data 124
- preclinical toxicological studies 64
- recommendations for uncertainty reduction 67
- publicity, for research 154
- “quality of life” protocol 23
- Raper, Steven 31, 32
- “reciprocal value” 93
- Recombinant Advisory Committee (RAC) 18, 22, 38
- cystic fibrosis trial approval (Crystal’s) 158
- familial hypercholesterolemia trial approval 157–8
- first gene transfer trial (Anderson) approval 156–7
- first-in-human trial approval pathway 20
- GAD gene transfer in Parkinson’s disease 110
- information available publicly 22
- OTCD study 32, 37–8
- risk classification, technical terms 40
- stable volunteers in studies 33
- uncertainty minimization 59
- waiving of normal review for glioblastoma agent 72, 83
- recommendations in book 184
- regulations for cell therapy 182
- regulations for gene transfer 19–20, 21–2, 188
 - centralized review 22
 - failure, in OTCD study 37–8
 - inclusionism, for early phase trials 73
- Institutional Biosafety Committee 22
- IRB *see* Institutional Review Board (IRB)
- recommendations 42
 - outside experts 42
 - violations 1
- regulators 19–21
- regulatory model, value, of phase 1 trial 91–2, 94
- research ethics 90–1
 - agenda for 186–7
 - principles 134
 - social value of study 90
 - transgenerational 187
- research ethics committee 21
- research policy, orientation and shift 24–5
- responsiveness, to host communities 137–9, 148
 - biological criteria for measuring, criticisms 137
 - conditions required 144
 - local utility of knowledge 138, 144
 - urgency 138, 140, 141, 144
 - definition 137, 143
- Fair Benefits *see* Fair Benefits policies for achieving 145–7

Index

- responsiveness, to host
 - communities (*Cont.*)
 - advance purchase agreements 145, 147
 - discriminatory pricing 145, 146, 147
 - intellectual property licensing 145, 146–7
 - pharmaco-philanthropy program 145–6
- presumption in gene transfer studies 139–43
 - autonomy argument 140, 142
 - polyvalence argument 140, 142
 - properties argument 140
 - trickle-down argument 140, 142
- reconciling early-phase gene transfer trials with 143–4
 - evidence against presumption on responsiveness 143–4
 - intervention able to be deployed 144
- responsiveness, to host
 - social/political and economic conditions 138
 - ultra-rare diseases 143
- retinoblastoma 13, 23
- retroviruses as vectors 11–12
 - integration near LMO2 51, 54
 - review of data on safety 59
- self-inactivating, risk minimization 57
- X-SCID, lymphoproliferative disease and 51
- rheumatoid arthritis 37
- risk(s)
 - AAV-GAD protocol 124–5
 - acceptable, defining 42–5
 - analogical strategy 43–4
 - OTCD study and 42–5
 - procedural strategy 44, 45
 - scientific information for 43
 - threshold 43
 - “best risk estimate” 55
 - classification, challenge of 39–41
 - hemophilia and gene transfer studies 3–4
 - OTCD study 39–41
 - recommendations 40–1
 - risk in technical terms 40
 - sociology of risk 40, 41, 42
 - compensated by collateral benefits 75
 - concept, product formula and 127
 - confidence levels
 - encompassed in 56
 - estimation in clinical trials, uncertainty and 55–7
 - evaluation 3, 128
 - effect on study design 3
 - hemophilia and gene transfer studies 3
 - risks to others 4
 - risks to volunteers 3–4
 - see also* risk assessment
 - evidentiary standards for trial initiation 116–17, 127
 - as forensic resource 31
 - gene transfer *vs* new drugs 52
 - justification, for translational trials 79–80
 - management *see* risk management
 - minimization strategies 57–8, 59–60
 - modeling/predicting 60
 - non-linear dose-toxicity curves 31–2
 - normalizing 41–2
 - OTCD study *see* OTCD study
 - scientific benefits *vs* medical risk 42
 - therapeutic *vs* nontherapeutic procedures 3–4, 23, 76
 - translational model of value and 99
 - translational trial practices 46
 - uncertainty and
 - see* uncertainty, and risk in gene transfer
 - “upper bound” estimate 56–7, 58, 113–14
- risk assessment 3
 - group participation in 44–5
 - hemophilia and gene transfer trials 3
 - recommendations 40–1
 - risks to others 4
 - risks to volunteers 3–4
 - study design affected by 3
 - see also* risk(s), acceptable
- risk management 67, 183
 - challenges 179
 - RNA interference 10
 - Rogers, Stanfield 8
 - Rosenberg, Steven 26, 156, 161
 - Royston, Ivor 72, 83
- safety in translational trials 31
 - preclinical toxicological studies publication 64
 - prioritization 61
 - purpose of phase 1 trials and 89
 - redundancy in systems 61
- safety symposia 59
- San Diego Cancer Center 72, 83
- Sawyer, Diane 154, 167, 171
- Scheie Eye Institute 153, 171
- scientific information, for acceptable risk definition 43
- selection of patients *see* subject selection
- self-criticism by researchers 170
- self-regulation, lapse, in OTCD study 38–9
- semen, gene transfer vector sequences 4
- sensationalism, medical 160
- serendipitous discoveries 101
- severity of illness, scaling of evidentiary standards for trial initiation 117
- Shope papilloma virus 8
- Small Business Patent Procedures Act 24
- social value, phase 1 trial 89–90, 103, 184
 - see also* humanitarian model of value
- societal value, of research 134, 184
- society, technology outstripping policies 189
- sociology/social nature of risk 40, 41, 42
 - minimization, “high-reliability organizations” 60
- somatic cell nuclear transfer 9, 180
- somatic cells, as gene transfer target 2, 10, 23, 27
- South Africa
 - guidelines for trials 137

Index

- stavudine licensing 147
- species specificity 54
- sponsors, of research 17
- stable volunteers 32–3, 42
- STAIR I 127
- standards
 - evidentiary, trial initiation
 - see initiation of human trials
 - immunological status
 - measurement 63
 - lack of, for viral vectors and dose 62–3
 - reference, viral vectors 63
 - role in organizing uncertainty 61–3
 - stringent value 58
 - for study design, need for 63
 - for supporting evidence, FDA 113
- status quo bias 186
- stavudine 147
- stem cell transfer 178
 - gene transfer comparisons 180–3
 - initiation of trials 181
 - in LMICs 182
 - Perin's study *see* Perin, Emerson
 - regulations and policy 182
 - scientific uncertainty 180
 - subject selection 181
 - technical complexity 180–1
- Stokes, Donald 95
- Straus, Stephen 32
- study design
 - direct benefits *vs* risk of early-phase trials 77–8
 - for efficacy *vs* risk 62
 - funding difficulties and scientists involved 16
 - group participation in 44–5
 - heterogeneity, phase 1 trials 79
 - need for standards/ uniformity 63
 - organizing uncertainty 61–3
 - pragmatic, drug trials 91
 - risk and uncertainty
 - minimization strategy 57
 - standardizing, for meta-analyses 66
 - subject selection 3
 - cautiousness, risk
 - minimization by 57
 - cell therapy trials 181
 - hemophilia trials 3, 57
 - medically stable volunteers 32, 42
 - oncology model 32
- Sugarman, Jeremy 112
- suicide genes 13
- supporting evidence, for gene transfer 111
 - stringency relationship with risk 111
- surrogate benefits of studies 82–3
- targeted cancer therapy 182
- technological optimism, culture of 73
- “technological sublime” 73
- Terheggen, H.G. 8
- terminal illness, evidentiary standards for trial initiation 117
- Texas Heart Institute 178, 181
- TGN1412 study 57, 67
- β-thalassemia 122, 134
- therapeutic gene transfer studies 23
 - vs* nontherapeutic procedures 3–4, 23, 76
- tiered-pricing
 - see discriminatory pricing
- tissue accessibility, phase 1 testing selection 100, 102
- tissue specimen archiving 63, 66
- Trade-Related Intellectual Property Rights (TRIPS) 64
- transgene 11, 54, 112
- transgenerational research ethics 187
- translational distance 117–19, 128, 184, 186
 - AAV-GAD protocol 124–7
 - appraisal of credibility of information for 122–4, 125
 - AAV-GAD protocol 126
 - bias and financial interests affecting 123
 - policies enhancing 123–4
 - recommendations 123–4
 - bridging, models and trial designs 121
 - confidence in predicting clinical outcome from laboratory observations 122
 - correspondence between preclinical/clinical studies 122, 125, 126
 - criticisms 118–19, 127
 - retarding medical innovation 127
 - external validity and 120–1, 125, 126
 - internal validity and 119–20, 125, 126
 - modest *see* modest translational distance, principle
 - principle 117–19, 122, 127
 - purpose of concept 118
 - source and control measures 125
- translational model of value 92–4
 - accrual of value by translational trials 95–6
 - applying 98–100
 - arguments/evidence supporting 94–7
 - characteristics 98–100
 - contingency plan 98–9
 - explicit description 98
 - flexible intervention 98
 - measurement of target effects 98
 - solid preclinical evidence base 98
 - stringency (risk/ complexity) affecting 99–100
 - circularity between clinic and laboratory 94
 - consent and 95
 - definition 93
 - discovery and innovation 95
 - diseases with tissue accessibility 100, 102
 - failure to produce biological response and 99–100
 - humanitarian model *vs* 103, 105

Index

- translational model of value
 (Cont.)
- iterative, reciprocal and
 lateral value 93, 96, 97
- novel interventions 95–6, 99
- non-novel agents *vs* 95–6,
 113–14
- objections to 100–3
 costs 100
- ethical limitations 102–3
- high-pay-off research
 excluded 101
- limiting opportunities for
 discoveries 101–2
- physical limitations 102
- practical limitations 100–1
- optimal *vs* obligatory 100
- regulatory model relationship
 95
- stringent assessment of risk/
 benefit 95
- translational oncology,
 methodological rigor,
 studies 120
- translational research 24, 25
 agenda setting 187
- benefit/risk assessment of
 diseases 3
- considerations for applying/
 reviewing 106
- criteria for initiation
 see initiation of human
 trials
- decline in trial volume 165,
 166
- difficulties 1–2
- discontinuities with non-
 clinical research 5
- ethical problems, gene
 transfer model 4
- gene transfer as model 4–5
- humanitarian model of value
 applied to 105
- justice/fairness *see* justice
 and translational trials
- management refinements
 needed 42
- optimism bias affecting 123
- organizations 4
- outcomes 114
- pace 189
- practical significance of 105–6
- results/performance and
 expectations 154–5
- reward cultures of medicine
 vs science 16
- “trial effects” 74
- trophic factors 182–3
- Tversky, Amos 186
- UK 22
- UK, translational clinical
 research centres 4
- uncertainty, and risk in cell
 transfer studies 180, 189
- uncertainty, and risk in gene
 transfer 51–1, 105, 112,
 117, 178–80
- agenda for 186
- animal data and 56
- causes 179, 180, 184
- complex composition (of
 agents) 54, 179
- gene transfer agent mode
 of action 53
- immune-based toxicity
 54–5
- long-term impacts 54
- nonlinear dose-response
 relationships 55
- passive *vs* active
 compositions 53
- species specificity 54
- as “companion to
 opportunity” 179
- confidence included with
 risk 56
- ethical frameworks 183–5
- implications of increased
 uncertainty 55
- organizing 58–61, 67
 design features 61–3
- “organizational learning”
 61, 62
- policies/practices to reduce
 59–60
- shortcomings in 59
- standards role 61–3
 see also OTCD study,
 risk/safety assessment
- of principles, risk justification
 57–8
- product formula and trial
 comparisons 56
- protective role of 186
- recommendations for
 “taming” 64–7,
 179–80
- across life cycle of
 protocols (vertical
 reforms) 64–5
- across multiple protocols
 (horizontal reforms)
 66–7
- implementation
 responsibility 66–7
- response to 55, 56, 57–8
- risk estimation in clinical
 trials 55–7
- strategic mobilization
 179–80
- stringent standard of value
 and 58
- “upper bound” estimate 56–7,
 58, 113–14
- University of Pennsylvania
 17, 31
- familial hypercholesterolemia
 trial (Wilson’s) 157
- OTCD study *see* OTCD
 study
- preclinical studies of Leber’s
 congenital amaurosis
 153
- University of Rochester 38
- “upper bound” estimate 56–7,
 58, 113–14
- vaccine development 148
- vaccine manufacturers,
 discriminatory pricing
 146
- vaccinia virus, as vector 12
- validity 5, 3, 90
 hemophilia and gene transfer
 3
- internal/external,
 translational distance
 see translational distance
- patient motivations for
 phase 1 trials, informed
 consent 80 *see also* value,
 of phase 1 trial
- value, of phase 1 trial 5, 3, 90,
 93, 183
- definition and assessment
 90–1, 91
- ethics review bodies’ caution
 over 106
- humanitarian model
 see humanitarian model
 of value

- progressive notion, *vs*
 - translational model 96
- regulatory model 91–2, 94
 - translational model
 - relationship 95
- in scientific literature 90
- social *see* social value
- translational model
 - see* translational model
 - of value
- Varmus, Harold 22, 27, 92
- venture capital 61
- Verma, Inder 39
- victimhood, adverse
 - expectations and 167
- viral vectors 11–12, 53
 - lack of standard for dose/potency 62–3
 - recombination 53
 - reference standard 63
 - risk minimization strategies 57
 - see also* individual viruses
- in vivo and ex vivo delivery
 - approach, gene transfer in 13
- volunteers
 - compassion for 72, 83
 - monitoring *see* monitoring of volunteers
 - phase 1 trials as medical opportunity 72–4
 - trials not optimized for safety 67 *see also* patients
- The Washington Post*, reports 157, 171
- website 192
- Weissmann, Irving 181
- Wiley database, gene transfer trials 97
- Wilson, James I, 31, 32
 - familial hypercholesterolemia trial 157–8, 159, 161, 162
 - financial conflict of interest 35–6
- OTCD study (Gelsinger)
 - see* OTCD study
- personal ambition and misconduct 34–5
- workshops, uncertainty/risk minimization 59–60
- World Health Organization (WHO) 141
- Worton, Ron 160
- Wynne, Brian 40
- X-SCID (X-linked severe immune deficiency syndrome) 1, 52
- Evans, Rhys 51
- gene transfer risk (*vs* drugs) 52
- lymphoproliferative disorders 5, 51, 54, 163
 - insertional mutagenesis role 51–2
 - reporting and monitoring 60
- regulation and 188
- xenotransplantation 182
- Yale University, stavudine 147