

# Bioethics Timeline

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# Objectives

- To describe a topography of bioethics
- To describe a timeline of developmental and inclusive approach to bioethics and research ethics training
- To have time for discussion



KOÇ  
ÜNİVERSİTESİ

❑ *Fogarty/NIMH funded federal training grants with establishment of a regional Summer Institute on Research Methodology and Bioethics in Health Science at Koc University in collaboration with Boston Children's Hospital and Harvard Medical School and Network of Faculty in Turkey*

✓ *Why a research ethics training complementary to research career development?*

RESEARCH METHODOLOGY  
AND ETHICS

# Research Capacity Development: Question of Sustainability

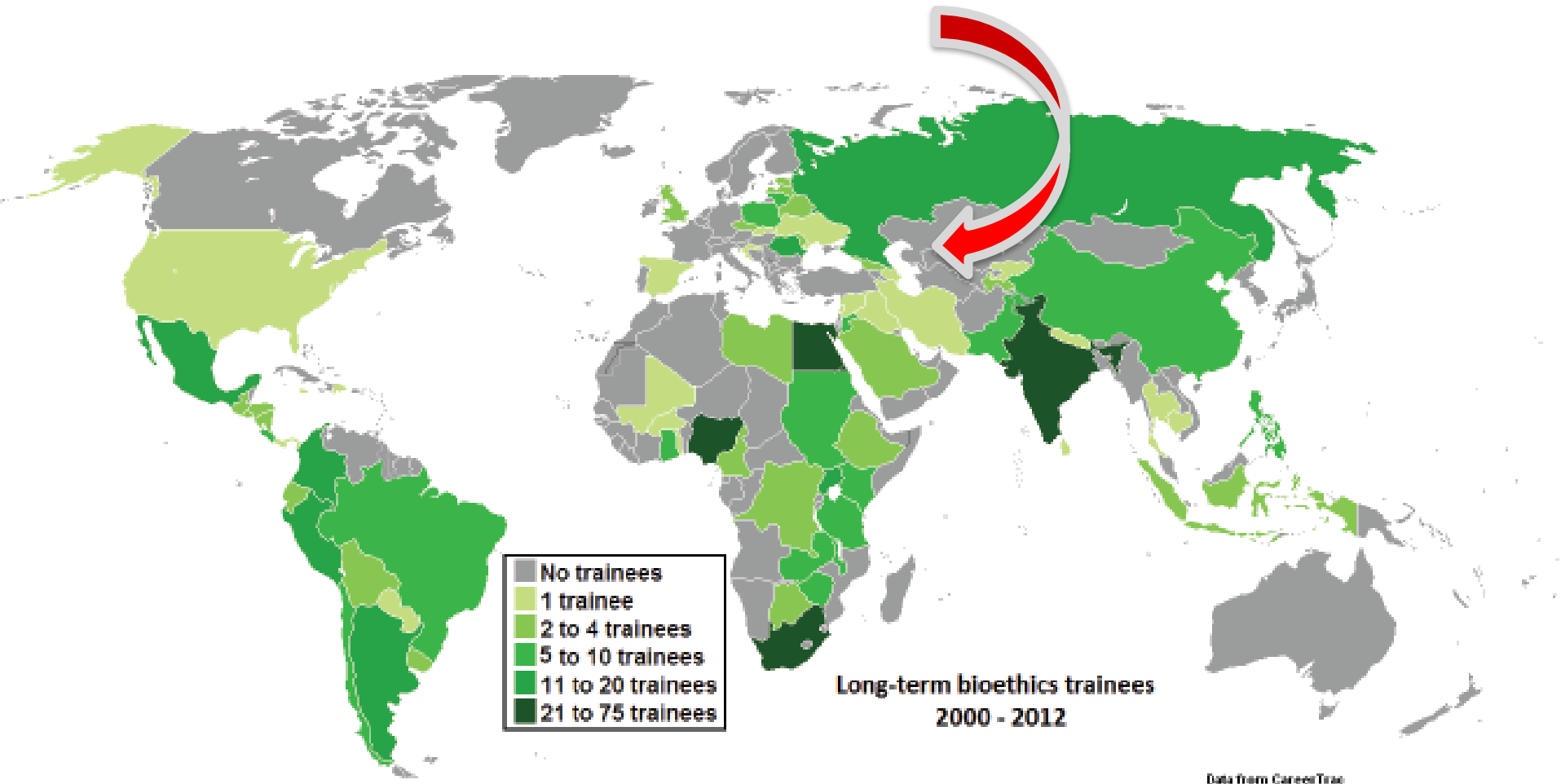
- ☐ Transparency
- ☐ Non-extractive institutional framework (cf., “Why Nations Fail?” by *Daron Acemoglu*)
- ☐ Freedom of expression
- ☐ Merit-based, generative systems
- ☐ Peer review
- ☐ Ethics review
- ☐ Responsible conduct

# Evolving International Research Ethics Landscape

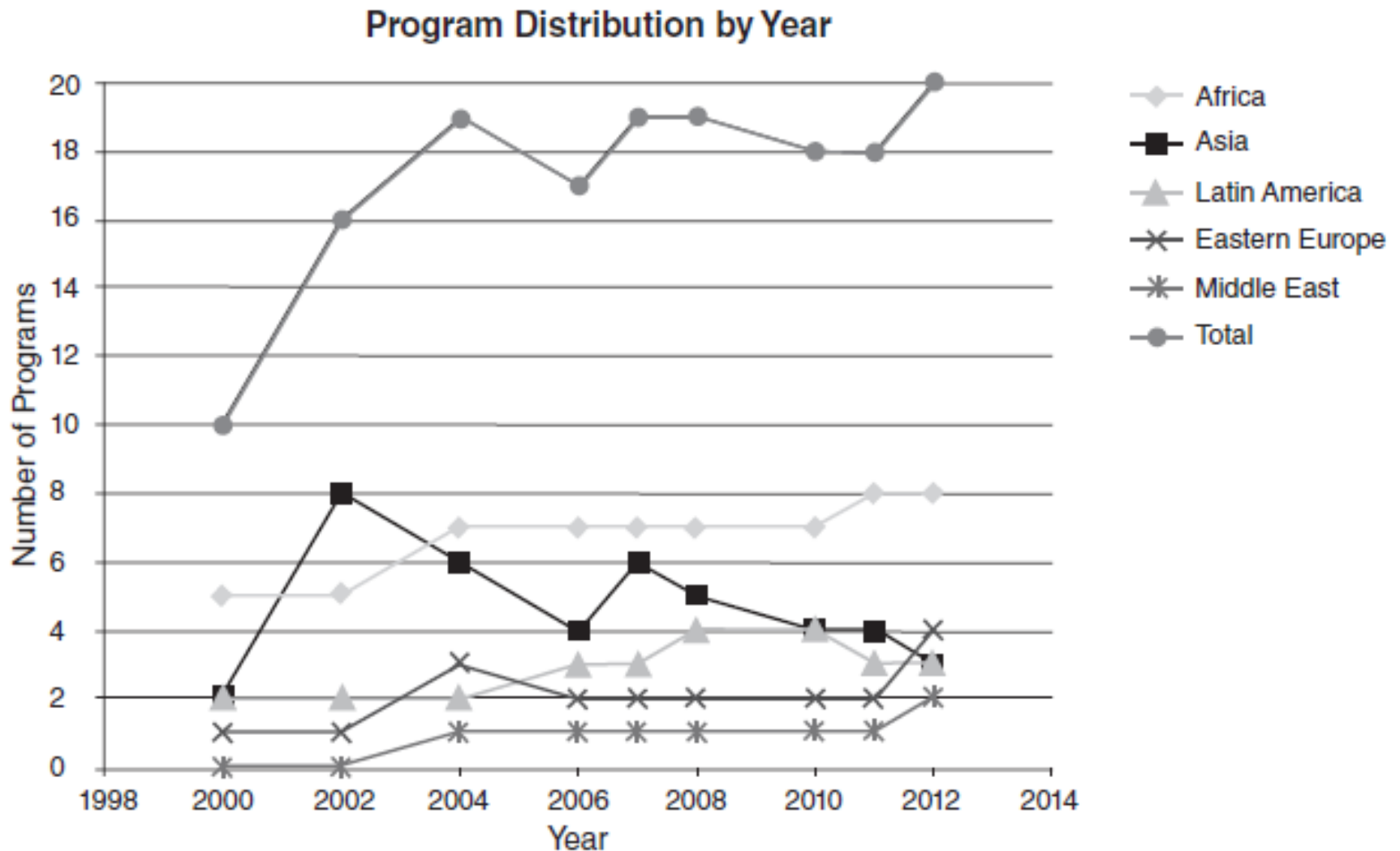
| Early concerns  | → | Transitions beginning late 1990s  | → | Current   |
|---|---|---|---|---|
| Exploitation, helicopter research                           |   | Responsiveness and post-trial planning to minimize exploitation   |   | Collaborative partnerships, benefit sharing, responsiveness   |
| Ethical imperialism   |   | Capacity building   |   | Partnership, community engagement, capacity building  |
| Inappropriateness of Western norms such as informed consent |   | Expanding commitment to individual informed consent, respect for permission of community or tribal leaders<br>Standards of care in study design |   | Continued commitment to improving informed consent everywhere<br>Standards of care, ancillary care, post-trial care |

- ❑ 1991 – Council for International Organizations of Medical sciences (CIOMS/WHO International Ethical Guidelines)
- ❑ 1993 - UNESCO International Bioethics Committee
- ❑ 1994 - AIDS AZT Clinical Trial 076
- ❑ 1997 – Lurie & Wolf, Angell NEJM Editorials
- ❑ 1999 – First Global Form on Bioethics Research
- ❑ 2000 – FIC/NIH International Research Ethics Grants initiated
- ❑ 2005 – UNESCO Declaration on Bioethics and Human Rights
- ❑ 2007 – Wellcome Trust's Ethics & Society Program
- ❑ 2013 – H3 Africa Initiates ELSI Grants

# International Bioethics Initiative established by Fogarty / NIH



# Fogarty / NIH Trainees in 5 regions

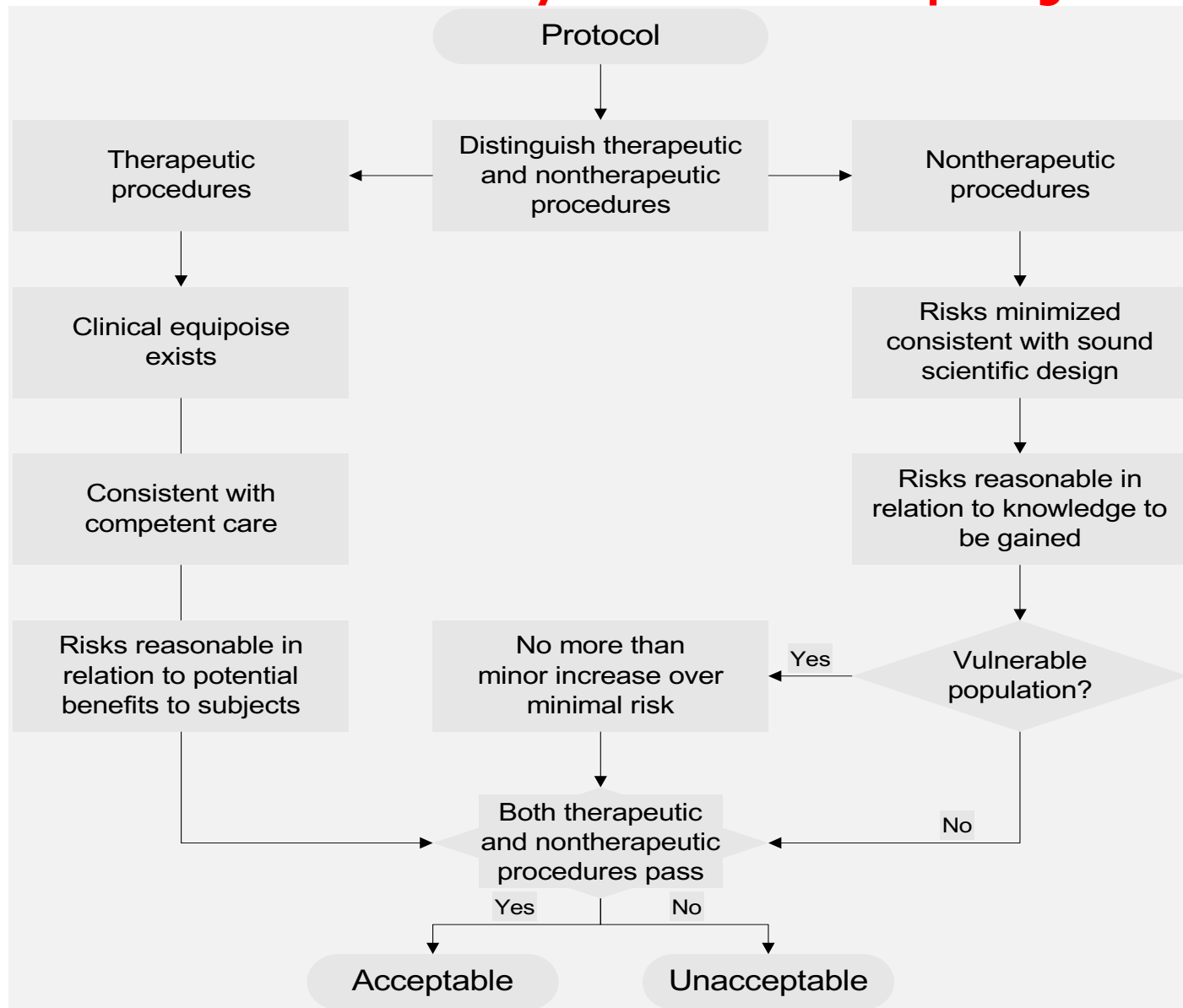


# “Ethics Continuum” for Inclusive and Responsible Conduct of Research

- ❑ Interpretation of burdens (subjects need protection) vs. benefits (subjects need access)
- ❑ Minimization of possibility of exploitation and ensure that rights and welfare of subjects are respected
- ❑ Scientific goals consistent with ethical principles:
  - Subject selection (minimize risks/maximize benefits)
  - Distributive justice: non-exclusion of vulnerable subjects due to inconvenience, without justification, and without careful airing of distributive burdens as well as the benefits of research
- ❑ An evolving research ethics framework: a balance between seven principles (often most difficult to assess in the case of most vulnerable subjects):
  - ✓ *Valuable scientific question*
  - ✓ *Valid scientific methodology*
  - ✓ *Fair subject selection*
  - ✓ *Favorable risk-benefit evaluation*
  - ✓ *Independent review*
  - ✓ *Informed consent*
  - ✓ *Respect for enrolled subjects*



# Benefit-harm analysis for all projects



# “Developmental Context” in Research Ethics

- ❑ The past informs the present
- ❑ Legacy of research on vulnerable children who suffered human rights abuses in the name of medical science
- ❑ There is linkage between Eugenics and Nazi Ideology
- ❑ Despite World War II → Institutionalization persists
- ❑ Institutions as Retreats → Repositories (*“Out of sight out of mind”*)
- ❑ Despite unique pioneers → Situations not prevented
- ❑ Vulnerability emerging as a generalized concept in terms of disparities, developing countries, ACEs, continuing stigma
- ❑ New challenges in terms of biotechnology, genomics, AI, Big Data, pharmaceuticals → Drivers of global research

# Political Justification trumps ethics...

- ❑ Guatemalan experiments occurred at a time when syphilis was taking a large toll in human life and undermining troops and security of the US.\*
- ❑ \*Though the Tuskegee and Guatemala experiments were similar, there was a key difference: In Tuskegee (1932-1972) researchers withheld treatment but never infected anyone and subjects who had the disease were followed to track its course but also were not treated.

# Bioethics Timeline-1

- ❑ **1939-45 - Nazi Experiments**
- ❑ **1946 - Nuremberg Trials**
- ❑ **1947 - Nuremberg Code Adopted.**
- ❑ **1944-70 - US Radiation Experiments**
- ❑ **1950s-1963. CIA Mind Control Program.** (Administration of LSD to unwitting subjects)
- ❑ **1956 - Willowbrook School Hepatitis Experiments** (exposed in 1972)
- ❑ **1961- Silent Spring** published by Rachel Carlson alerts against harmful effects of DDT on environment
- ❑ 1961-62 – Stanley Milgram “Electric Shock” Experiments. People are willing to do things that they consider to be morally wrong when following orders of an authority (Obedience to Authority published in 1974).
- ❑ **1962 - Thalidomide revelations 1963 - Seattle Dialysis Selection Committee**
- ❑ **1965 - Medicare and Medicaid enacted 1964**
- ❑ **1965 - Declaration of Helsinki adopted by the World Medical Association.** Informed consent in studies involving human subjects. (Multiple revisions, most recent in 2013, not recognized by the US)
- ❑ **1966 – Harry Beecher’s Article in the NEJM.** “Ethics and Clinical Research”. Exposes 22 unethical studies in biomedicine, including the Tuskegee syphilis study and the Willowbrook School hepatitis study
- ❑ **1969 - Hastings Center Established.** Dan Callahan, PhD Phil. Harvard, and Willard Gaylin, Psychiatrist, Columbia University
- ❑ **1971 – A Defense of Abortion.** Judith Jarvis Thomson argues for permissibility of abortion (regarded as precursor to Roe v. Wade)
- ❑ thought they were being treated for “bad blood”
- ❑ **1973 - Roe v. Wade.** US Supreme Court 7-2 decision, majority opinion written by Justice Harry Blackmun
- ❑ **1971 – A Defense of Abortion.** Judith Jarvis Thomson argues for permissibility of abortion (regarded as precursor to Roe v. Wade)
- ❑ **1972 – USPHS Tuskegee Study Exposed.** Began 1932, study of effects of untreated syphilis in 400 African American airmen. Researchers withhold treatment even when penicillin became widely available, subjects never told they were in an experiment, most thought they were being treated for “bad blood”
- ❑ **1973 - Roe v. Wade.** US Supreme Court 7-2 decision, majority opinion

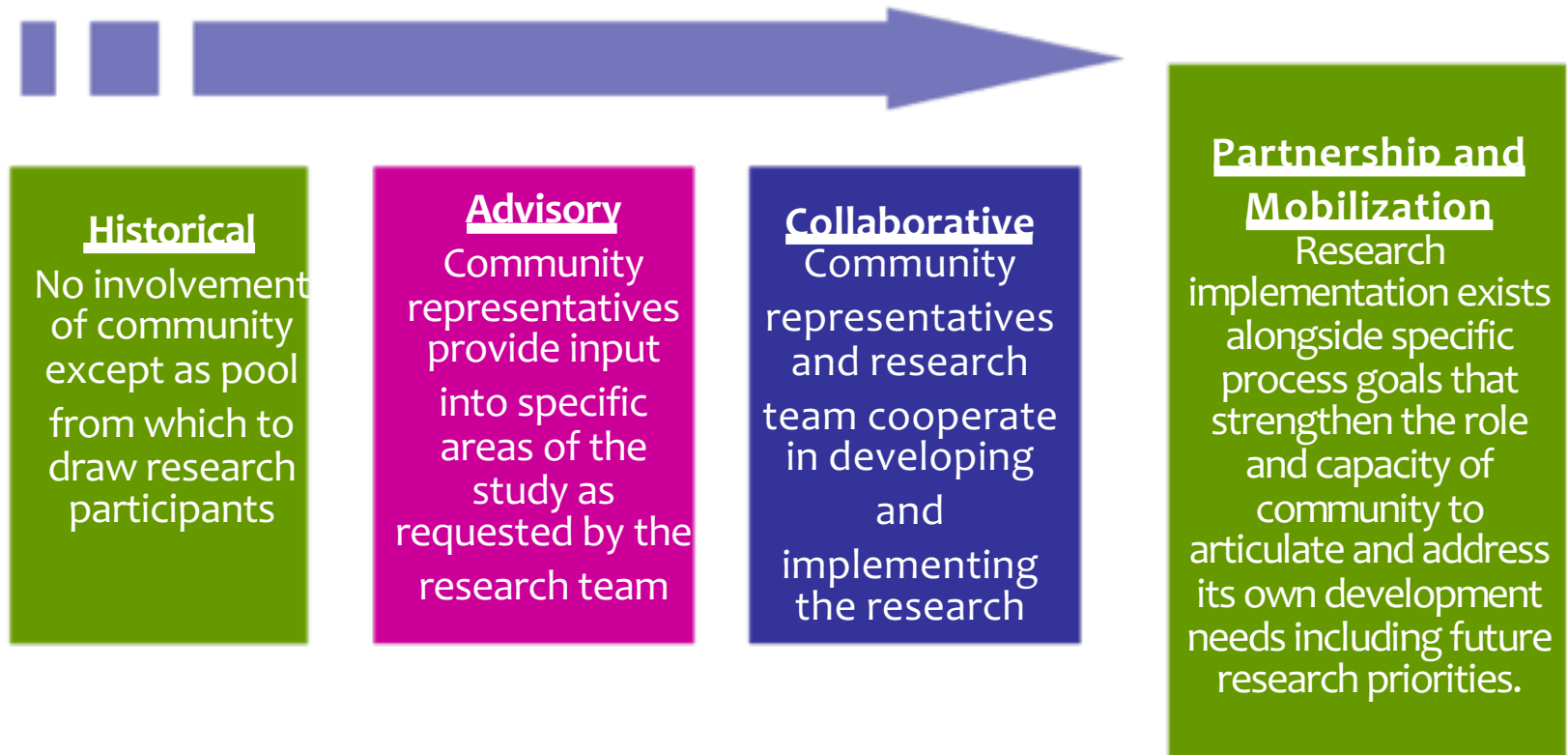
# Bioethics Timeline-2

- ❑ **1974 – National Research Act, US Congress enacted** - in response to public outcry to Tuskegee and the *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* (first national bioethics commission) is established. The act authorizes federal agencies to develop human research regulations, e.g., 45 CFR 46, 21 CFR 50, 54, 56.
- ❑ Current regulations includes 5 subparts:
- ❑ **1. Subpart A is the basic protections for all human subjects research under HHS** - revised in 1981 and 1991, with amendments in 2005.
- ❑ Three other subparts provide added protections for vulnerable groups:
  - 2. Subpart B, issued in 1975, and revised in 2001, provides additional protections for pregnant women, human fetuses, and neonates**
  - 3. Subpart C, issued in 1978, provides additional protections for biomedical and behavioral research involving prisoners**
  - 4. Subpart D, issued in 1983, provides additional protections for children**
  - 5. Subpart E, issued in 2009, requires registration of Institutional Review Boards (IRBs) to conduct review of human research studies supported by HHS.**
- ❑ **1974 – William Summerlin – First Data Fabrication exposed.** Uses a marker to make black spots on white mice at Sloan Kettering while developing a technique for transplanting skin grafts.
- ❑ **1976 – Karen Ann Quinlan Case**
- ❑ **1976 – Tarasoff v. Regents of University of CA**
- ❑ **1978 – First IVF Baby born.** Baby Louise Brown
- ❑ **1979 – Belmont Report released.** Most important document for contemporary IRB guidance, by National Commission, identifies 3 fundamental principles for human studies:
  - Respect for Persons (autonomy)
  - Beneficence, non-maleficence
  - Justice (distributive)
- ❑ **1980 – Diamand v. Chakrabarty Case.** The US Supreme Court rules that a genetically modified bacterium can be patented because it is the product of human ingenuity, broadening intellectual property protections
- ❑ **1980 – Bayh-Dole Act.** Allows researchers to patent inventions developed with federal funds; amended as Technology Transfer Act in 1986.
- ❑ **1981 – Definition of Death adopted**
- ❑ **1981 – John Darsee Case.** A postdoctoral fellow at Harvard is accused of fabricating data including a paper in Nature. Dr. Darsee goes on to practice medicine

# Application of the Belmont Report Guidelines

| Ethical Principle       | Ethical Rule   |
|-------------------------|--|
| Respect for persons     | Obtain the informed consent of prospective research subjects   |
|                         | Protect the confidentiality of private information   |
| Beneficence             | Therapeutic procedures must satisfy clinical equipoise   |
|                         | Risks of non-therapeutic procedures must be (1) minimized and (2) reasonable in relation to knowledge to be gained |
| Justice                 | Subject selection procedures must be fair  |
|                         | Compensate subjects harmed as a result of research participation   |
| Respect for communities | Respect communal values, protect and empower social institutions   |
|                         | Where applicable, abide by the decisions of legitimate communal authority  |

# Application of Norms for “Community Inclusion” in Research



# Bioethics Timeline-3

- ❑ **1982 – Betrayers of Truth published.** Era of fraud busting begins
- ❑ **1982 – Baby Doe Case.** Born with Down syndrome, parents decline life salvaging surgery, don't want child to grow up with ID; Indiana Supreme Court rules in favor of parents, 1983 President Reagan requests Secretary of HHS to issue regulations to prevent death of children with disabilities, AAP challenges.
- ❑ **1983 - US Supreme Court decision “Federal Government has no power to overrule parental decisions”.** However, in 1985 President Reagan signs law to withhold Federal funding from states not complying with surveillance of NICUs.
- ❑ **1980-83 – Steven Breuning.** A NIMH funded researcher at the University of Pittsburgh fabricated and falsified data on 24 papers on efficacy of antipsychotics in individuals with intellectual disability. Barred from receiving grants, but subsequently first researcher to be criminally prosecuted and sentenced to 60 days imprisonment and 5 years probation
- ❑ **1983 – Elizabeth Bouvia.** Paralyzed with CP and degenerative arthritis, asks to be starved in hospital, refused, court sides with hospital, resists NG tube claims battery, loses, on appeal wins right to have NG tube removed, but decides not to commit suicide, alive today
- ❑ **1985-89 – Larry McAfee.** Paralyzed in MVA, on ventilator, in NH, wants to die. Georgia Supreme Court sides with him, with public attention he gets help, out of NH and into job training, changes his mind. (Dies of pneumonia in 1995)
- ❑ **1989 – PHS Office for Scientific Integrity and the Office of Scientific Integrity Review established.** (reorganized in 1992 as Office of Research Integrity).
- ❑ **1989 – NAS Published on Being a Scientist**
- ❑ **1990 – Nancy Cruzan Case.** In 1983, Nancy, 25, in vegetative state after MVA, fetal posture, 4 years of no recovery, parents and husband suggest she be removed from feeding tube, State of Missouri refuses, in 1990 US Supreme Court 5-4 rules that people have right to refuse medical treatment under Due Process unless evidence of Living Will, family finds more ‘proof’ of Nancy’s implicit desire, life support removed (father commits suicide 6 years later ‘from emotional toll of 6 years legal battle)
- ❑ **1990 – Human Genome Project.** 5% of budget for Ethical, Legal, Social Implications, ELSI).
- ❑ **2003 - Human Genome Project completed**
- ❑ **2008 - President Bush signs Genetic Information Non-Discrimination Act, GINA)**
- ❑ **1990 – First Congressional investigation of conflict of interest.** Pharmatec v. University of Florida
- ❑ **1991 – All US government agencies, except EPA, accept one regulatory framework, known as “the common rule” (45 CFR 46)**
- ❑ **1992- NAS published Responsible Science: Ensuring the Integrity of the Research Process.** The report estimates the incidence and causes of misconduct, proposes a definition and measures to prevent it



# Bioethics Timeline-4

- ❑ **1987 – Baby M Case.** Sterns place ad for surrogate (Mrs. Stern has MS), Mary Beth Whitehead signs contract, artificially inseminated, Mar 1986 Baby M born, day after Mary Beth asks for child back, claiming she is biological mother, 1987 NJ Supreme Court awards Sterns custody “Best interests of child” analysis, 1988 NJ Supreme Court invalidates surrogacy contracts, Sterns keep baby, Mary Beth gets visitation rights
- ❑ **1994 – Oregon Assisted Suicide Legislation.** Oregon approved Death with Dignity Act, legalizing physician-assisted suicide (for terminal illness). 1997 Oregon voters approve, 1998, 1<sup>st</sup> legal physician assisted suicide in the US (2002, Netherlands, 1<sup>st</sup> nation to legalize euthanasia, also legal in Washington, 2008, and Montana, 2009). 2006, US Supreme Court uphold law in *Gonzales v. Oregon* (are vulnerable populations at disproportionately higher risk?)
- ❑ **1994 – Advisory Committee on Human Radiation Experiments (ACHRE).** President Clinton authorizes release of 1.6 m classified records, some describe radiation experiments from 1940-1970s, many people, many vulnerable unknowingly injected with radiation doses to assess health effects for Cold War Studies (incl. minorities, children, elderly, prisoners, patients) often leading to permanent harm and disability
- ❑ **1996 – Dolly the Sheep.** Born in Edinburgh, 1<sup>st</sup> mammal cloned by Ian Wilmut from an adult somatic cell, lives 6 years
- ❑ **1998 – Human Embryonic Stem Cells.** Dr. James Thompson, Wisconsin, isolates human embryonic stem cells, public outcry. 2001, President Bush limits govt. funding to existing stem cell lines, no new embryos allowed. In 2007 – James Thompson induces pluripotent adult cells “preprogrammed” to stem cells, diminishes need for embryonic stem cells. In 2009 – President Obama signs executive order reversing President Bush’s policy.
- ❑ **1999 – Dr. Kevorkian Convicted.** Helps woman recently diagnosed with Alzheimer’s to commit suicide. Between 1990-1998 had assisted deaths of 130 patients all supposed to be terminally ill (most patients females)
- ❑ **1999, Jesse Gelsinger Case.** Jesse, 18 year old with ornithine transcarbamylase deficiency controlled with diet and medications, enrolled in clinical trial U Penn for 1<sup>st</sup> Gene Therapy, 4 days later dies of massive immune response. Failure to report prior side effects, failure to report deaths in animal trials on informed consent form, financial conflicts of interest
- ❑ **1999 – HIV/AIDS Vaccine Trials.** NIH establishes HIV Vaccine Trial Network (HVTN), international collaborative, incl. developing countries to avoid double standards
- ❑ **2003 –Partial-birth Abortion Ban Act.** President Bush signs partial-birth Abortion Ban Act into law prohibiting late-term abortions (usually 2<sup>nd</sup> trimester)



# Ethics of Exclusion: *Persons with Developmental Disabilities*

- ❑ Argument: Do not have autonomous capacity to make informed choices
- ❑ Need: Facilitate their research participation with adequate protections especially if benefits anticipated (Helsinki revision, 2013)
- ❑ Need to be included in research that can bring them direct benefit especially when no other comparable group can help address the scientific questions
- ❑ Federal guidelines: Require inclusion of children, women and minorities. No such guidelines to prevent arbitrary exclusions of individuals with ID based on convenience and cost
- ❑ Distributive justice is a pivotal ethical principle: Individuals with ID face disproportionately higher burdens and need to participate in studies that may benefit them
- ❑ Greater awareness of this ethical paradox needed: Researchers, RECs, and funding agencies need to urgently redress this imbalance.

# Eugenics Movement in the US: Prequel to Buck v. Bell

- ❑ Beginning with Connecticut (1896) many states enacted laws with eugenic criteria prohibiting anyone from marrying who was “epileptic” or “feeble-minded.”
- ❑ Charles Davenport (1898) director of Cold Spring Harbor research station, established the Station for Experimental Evolution (1904), precursor to the Eugenics Record Office (ERO) (1910).
- ❑ The ERO collected family pedigrees and concluded that those who were unfit came from economically and socially poor backgrounds. Eugenacists began to lobby for solutions to the problem of the “unfit.” Davenport favored immigration restriction and sterilization as primary methods. Others favored segregation, and some even entertained the idea of extermination. Their methodology – although flawed - is regarded as legitimate research.
- ❑ In 1907, Indiana became the first to adopt legislation aimed at compulsory sterilization of the “unfit,” later overturned by the Indiana Supreme Court in 1921.
- ❑ In Buck v. Bell, the U.S. Supreme Court upheld the constitutionality of a Virginia law allowing for the compulsory sterilization of patients of state mental institutions in 1927.
- ❑ By 1930s, more than 30 states had passed laws often with an expanded list of hereditary defects, including alcoholism and drug addiction, and even blindness and deafness. They were challenged and rarely enforced, except California and Virginia. By 1935, 20,000 sterilizations were performed in the US, nearly half in California

# Buck v. Bell (1927), US Supreme Court

- ❑ In the US Supreme Court, Oliver Wendell Holmes, Jr., then in his mid-80s, wrote the majority opinion that forced the sterilization of a woman claimed to be of below average intelligence (The Supreme Court upheld by 8-1 the sterilization bill).
- ❑ In support of his argument he noted that the interest of the States in a "pure" gene pool outweighed the interest of the Individuals in their bodily integrity.

# Thank you

