Clinical Trial Basics De-Coded

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Disclosure Information

I have the following financial relationships to disclose:

Consultant for: Vaccinex, Celgene, Bristol Meyers Squibb, AstraZeneca, Amgen, Syndax, Molecuvax, eTHeRNA, Peregrine, Bayer, Gritstone, Medimmune, Abbvie, Replimune, Bristol-Myers Squibb, Roche, Genentech, Macrogenics, Lilly, Chugai, Silverback

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Under a licensing agreement between Aduro Biotech, and the Johns Hopkins University, the University and Dr. Emens are entitled to milestone payments and royalty on sales of a GM-CSF-secreting breast cancer vaccine. The terms of these arrangements are being managed by the Johns Hopkins University in accordance with its conflict of interest policies

What is Clinical Research?

Clinical research is research involving human subjects:

Research: “any activity designed to test a hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalizable knowledge, which may be expressed in theories, principles, and statements of relationships.”

Human subject: “a living individual about whom an investigator conducting research obtains with data through intervention or interaction with the individual or identifiable private information.

(45 CFR 46.102)

Human Subjects Research

- intervention: the procedures through which data are gathered (blood draws, CT scans, etc) and manipulations of the subject or the subject's environment that are performed for research purposes

- interaction: includes communication or interpersonal contact (interviews, questionaires) between the researcher/research team and the subject

Human Subjects Research

Private Information (covered by HIPAA):

- includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public

- is individually identifiable where the identity of the subject may be easily determined or is already associated with the information

Why the Need for Human Research Protections?

Tuskeegee Syphilis Study 1932-1971: designed to make treatment available to African American men with syphilis even though there was no effective treatment

- subjects were recruited without their consent
- misinformation about procedures
- penicillin shown to be effective in 1942, but subjects were denied antibiotics and prevented from obtaining treatment from military and local physicians

US Food, Drug, and Cosmetic Act of 1938

- 107 people died after taking the cold remedy sulfanilamide, which contained anti-freeze
- US Food, Drug and Cosmetic Act was passed in 1938 to protect the public
- established quality standards for food, drugs, medical devices, and cosmetics manufactured and sold in the US

Nuremberg Code 1947

- resulted from the investigation/trial of Nazi physicians and scientists conducting human subjects research during WWII
- at that time there were no guidelines for human subjects research
- defined a set of ethical principles for human subjects research
  - informed consent is required
  - research should be based on prior animal work
  - risks should be justified by potential benefits
  - researchers conducting human subjects research must be qualified to do it
  - physical and mental suffering should be avoided
  - expected death/severe injury from the study intervention is unacceptable

Limitations of Nuremberg Code

- interpreted as a judgement of the Nazi physicians and scientists
- thus had little impact on research conducted in the US
- not adopted as a law
- applied only to non-therapeutic human subjects research

Declaration of Helsinki 1964

- Code of ethics developed by the World Medical Association, now the World Health Organization
- Broader than the Nuremberg Code
- Developed to address the ethical issues of conducting therapeutic human subjects research
- Recommended informed consent
- Set the foundation for an IRB requirement
- Journals required all published research to adhere to guidelines defined by the Declaration of Helsinki

National Research Act of 1974

- Resulted from hearings conducted by the US Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, resulted in 45 CFR 46, which was revised in the late 1970's, the early 1980's, and in 2018
- **published as the COMMON RULE in 1991 (issued by DHHS)**
- widely adopted by federal agencies and others who fund and conduct research

- Purpose:
  - Identify basic ethical principles underlying the conduct of human subject research
  - Develop guidelines to ensure the conduct of human subjects research in accordance with those principles

2018 Changes to the Common Rule

- Aim to strengthen protections for study subjects and lighten administrative workloads for researchers
- Changes required as of January 21, 2019 apply to any institution who uses federal funds to conduct research:

  --revised consent forms must quickly/clearly capture the research study: indexing at the top of the page, disclosure of clinically relevant research results

  --minimal risk studies no longer require annual IRB review

  --one single IRB will oversee multi-site studies (by January 2020)

  --de-identified specimens currently exempt

  (concern re: ID by sequence info etc)

Belmont Report in 1979

- issued by National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- designed to resolve ethical issues that surround the conduct of human subjects research
- all principles delineated in the report have equal weight:
  - respect for persons:
    - requires informed consent and respect for privacy
  - beneficence: minimize harm and maximize benefit
  - justice: treat all fairly and ensure burdens and benefits are shared equitably
    - extra attention/safeguards for vulnerable populations or populations of convenience

International Conference on Harmonization (ICH) in 1990

- joint regulatory/industry conference for process improvement of global drug development across the US, Europe, and Japan
- establishes a common set of rules/regulations for conducting international human subjects research
- conference convenes periodically to update the guidelines
- established the rules/regulations for **GOOD CLINICAL PRACTICE**
- defines the standards for the design, conduct, performance, monitoring, analyses, and reporting of research
- established for drug studies but provides norms for best practices in conducting all human subjects research

Observational Studies: COHORT STUDIES

- groups of human subjects followed over time
- aim to define the incidence and investigate the potential causes of a conditions
- may be prospective, where an investigator chooses a sample group and measures characteristics in each subject over a period of time that might predict outcomes
- may be retrospective, where the data collection and follow up has happened in the past, requires that adequate data be available

Observational Studies: CROSS SECTIONAL STUDIES

- similar to cohort studies except that all measurements are made at one time point with no follow up
- designed to describe variables and their prevalence (distribution patterns)
- advantage: fast and inexpensive since no follow up or waiting time to monitor for outcome

Observational Studies: CASE-CONTROL STUDIES

- Two groups of people evaluated for a given outcome

- Designed to compare the prevalence of risk factors for a certain characteristic or disease in research subjects with the disease (“cases”) and in research subjects without the disease

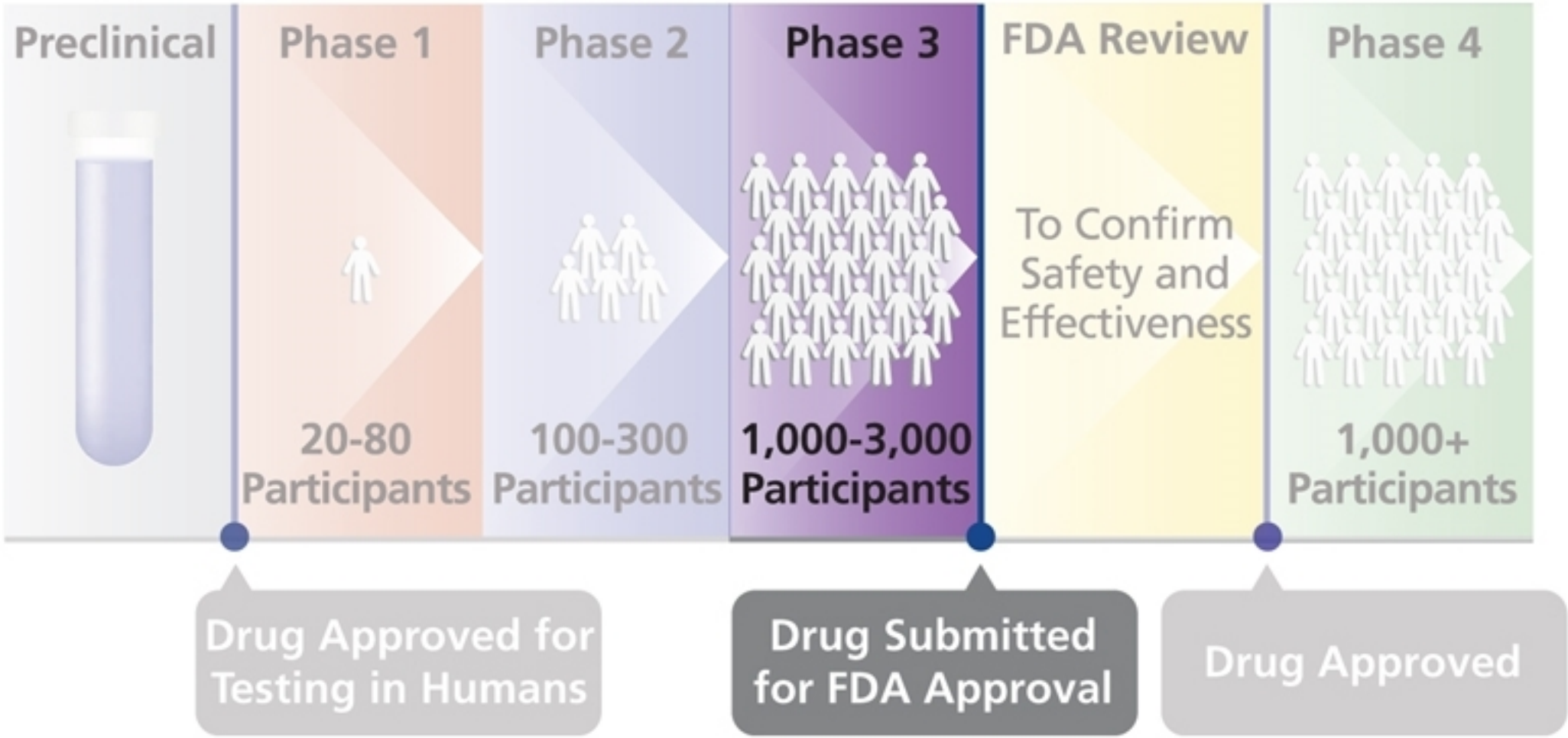
  --Group A: “cases” or a group of people with a certain characteristic or disease

  --Group B: “controls” or a group of people without that same characteristic or disease

Interventional Clinical Research Studies

- designed to evaluate the effects of an intervention
- can demonstrate causality/association
- examples:
  --behavior modification: for example a walking program to alleviate cancer-related fatigue
  --drug: investigational drug or studying a drug for off-label use
  --device: investigational device

Phases of Drug Development: Preclinical to Clinical



Phase 0 Clinical Trials

- performed in humans
- designed to speed up and streamline drug development
- exploratory studies that use only a few doses of a new drug in very small numbers of patients in order to:
    --test whether the drug reaches the tumor
    --test how the drug acts in the body
    --test how cancer cells respond to the drug in vivo
- limited risk and virtually no chance of benefit to the patient

Phase 1 Clinical Trials: Is the Drug Safe with Potential Clinical Activity?

- frequently first in human studies of a new drug
- goal is to identify a dose that is safe and potentially clinical active
- historically goal was to identify maximum tolerated dose (MTD), in the modern era the goal is to determine the safe and optimal biologic dose (OBD) based on assays that evaluate whether the drug hits its target
- historically clinical activity was not a goal but in the modern era early signals of clinical activity are a goal of phase 1 clinical trials

Phase 2 Clinical Trials: Does the Drug Have Measurable Clinical Activity? Is it Safe?

- designed to evaluate clinical signals for drugs that show evidence of safety and activity in phase 1 trials
- may be single arm or randomized, may be placebo-controlled
- potential endpoints: ORR, TTP, DFI, QOL
- generates additional safety data

Phase 3 Clinical Trials: Is the Drug Better than or Equivalent to the Current Standard of Care? Is the drug safe?

- patient population typically defined in detail (may not reflect real-world practice)
- typically randomized
- often placebo-controlled
- may be double-blind
- results in a data set that the FDA can evaluate for a new drug approval

Phase IV Clinical Trials: Post-Marketing Surveillance

- additional safety data (very rare but serious side effects may emerge, long-term side effects may emerge)
- additional clinical efficacy data
- quality of life data (now frequently required in Phase III)
- cost-effectiveness

What is an Investigational New Drug Application (IND)?

- a document filed with the FDA to support the investigation of an investigational drug, or sometimes the investigation of a marketed drug
- must contain information in three major areas:

  --animal pharmacology and toxicology studies: preclinical data to permit an assessment of whether the product is reasonably safe for initial testing in humans

  --previous human use of the drug product

  --chemistry, manufacturing and control: information describing the composition, manufacturer, stability, and controls for producing the investigational agent consistently

  --clinical protocols and investigator information—allows assessment of risk to study participants, qualifications of the investigator, and commitment to obtain informed consent, submit for IRB review, and adhere to investigational new drug regulations

Clin Cancer Res. 2019 Feb 1;25(3):1000-1011. doi: 10.1158/1078-0432.CCR-18-0963. Epub 2018 Nov 8.

IND-Enabling Studies for a Clinical Trial to Genetically Program a Persistent Cancer-Targeted Immune System.

Puig-Saus C[1,2], Parisi G[3,2], Garcia-Diaz A[3,2], Krystofinski PE[3,2], Sandoval S[3,2], Zhang R[3,2], Champhekar AS[3,2], McCabe J[3,2], Cheung-Lau GC[3,2], Truong NA[3,2], Vega-Crespo A[3,2], Komenan MDS[3,2], Pang J[3,2], Macabali MH[3,2], Saco JD[3,2], Goodwin JL[4], Bolon B[5], Seet CS[3], Montel-Hagen A[6], Crooks GM[2,6,7,8], Hollis RP[9], Campo-Fernandez B[9], Bischof D[10], Cornetta K[10], Gschweng EH[9], Adelson C[8], Nguyen A[3,2], Yang L[2,8,9], Witte ON[8,9,11], Baltimore D[12], Comin-Anduix B[2,13], Kohn DB[9,14], Wang X[15], Cabrera P[3,2], Kaplan-Lefko PJ[3,2], Berent-Maoz B[3,2], Ribas A[1,2,8,11,13].

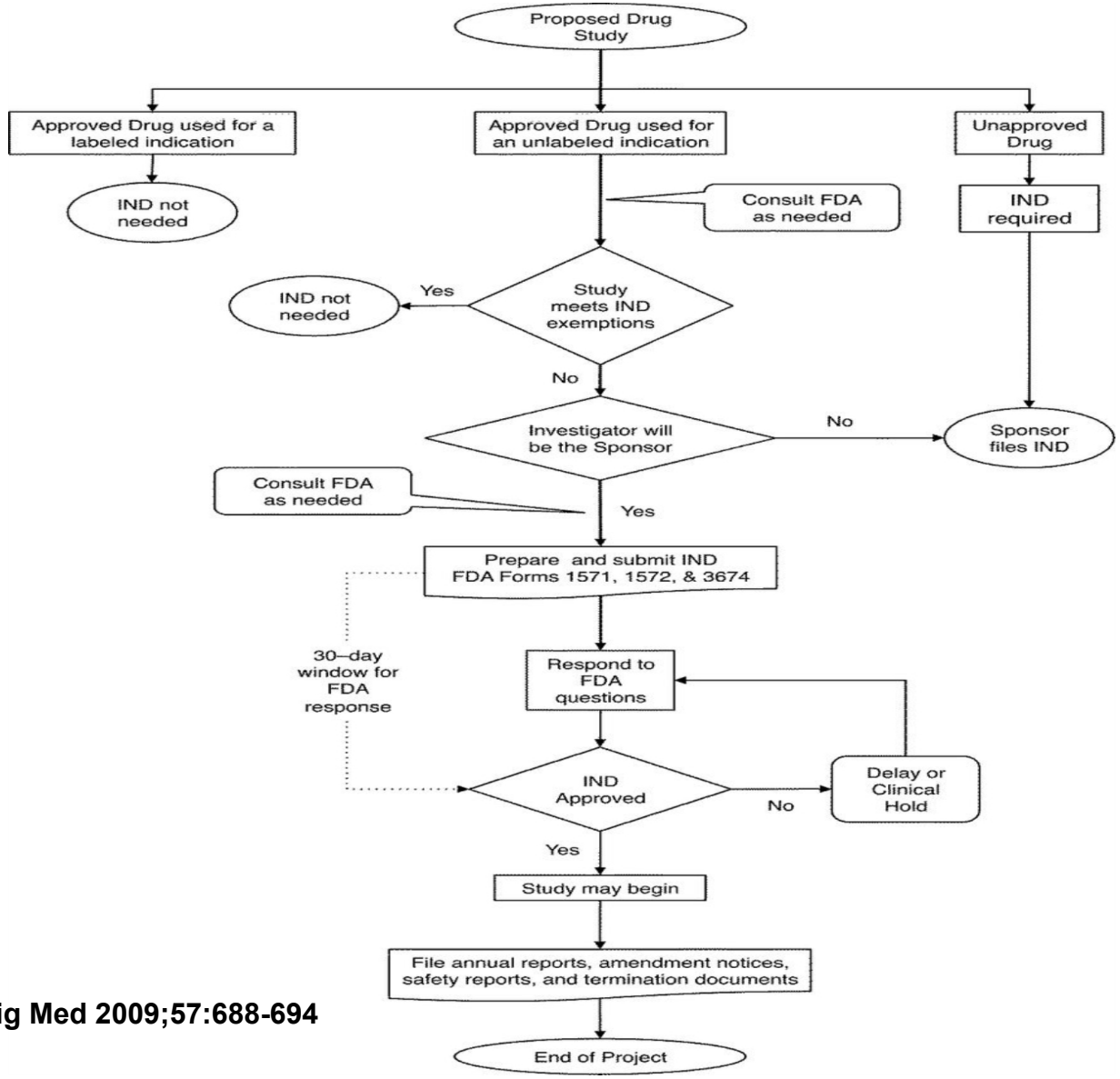
PURPOSE: To improve persistence of adoptively transferred T-cell receptor (TCR)-engineered T cells and durable clinical responses, we designed a clinical trial to transplant genetically-modified hematopoietic stem cells (HSCs) together with adoptive cell transfer of T cells both engineered to express an NY-ESO-1 TCR. Here, we report the preclinical studies performed to enable an investigational new drug(IND) application.

EXPERIMENTAL DESIGN: HSCs transduced with a lentiviral vector expressing NY-ESO-1 TCR and the PET reporter/suicide gene HSV1-sr39TK and T cells transduced with a retroviral vector expressing NY-ESO-1 TCR were coadministered to myelodepleted HLA-A2/K^{b}mice within a formal Good Laboratory Practice (GLP)-compliant study to demonstrate safety, persistence, and HSC differentiation into all blood lineages. Non-GLP experiments included assessment of transgene immunogenicity and *in vitro* viral insertion safety studies. Furthermore, Good Manufacturing Practice (GMP)-compliant cell production qualification runs were performed to establish the manufacturing protocols for clinical use.

RESULTS: TCR genetically modified and *ex vivo*-cultured HSCs differentiated into all blood subsets *in vivo* after HSC transplantation, and coadministration of TCR-transduced T cells did not result in increased toxicity. The expression of NY-ESO-1 TCR and sr39TK transgenes did not have a detrimental effect on gene-modified HSC's differentiation to all blood cell lineages. There was no evidence of genotoxicity induced by the lentiviral vector. GMP batches of clinical-grade transgenic cells produced during qualification runs had adequate stability and functionality.

CONCLUSIONS: Coadministration of HSCs and T cells expressing an NY-ESO-1 TCR is safe in preclinical models. The results presented in this article led to the FDA approval of IND 17471.

IND Flow Chart for Investigator-Sponsor



M. E. Blair Holbein J Investig Med 2009;57:688-694

Who is on a Clinical Research Team?

- Sponsor
- Principal Investigator
- Statistician
- Sub-Investigators
- Clinical Research Nurse
- Clinical Research Coordinator
- Regulatory Coordinator
- Clinical Research Program Manager
- Biospecimen Specialist
- CRO/Monitor

21 CFR 312.60

The principal investigator is responsible for ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights and welfare of the research subjects under the investigator's care; and for the control of the drugs under investigation.

Questions?

Thank you!