

Nano-drug Clinical Trials: Informed Consent and Risk Management Through Blockchain

Yousef Haik and Ilias Bantekas

Abstract

Drug bearing nano-shells that can be utilized for targeted drug delivery have been shown to enhance the therapeutic index by increasing the drug concentration in diseased tissue and reducing the toxicity in normal tissue. The controllability of the drug bearing shell size provides predictability measure for the amount of drug payload per shell which improves the administration of the therapeutic dose. The FDA approved different formulations for clinical use in metastatic and recurrent breast cancer, among other diseases. At the moment, some of these formulations are the subject of international clinical trials. Informed consent is legally mandated in administering drug bearing nano-shells. The risks of the new formulations, as with all new technologies, are not well known and continue to be the subject of intensive research, thus exacerbating the existing informed consent legal issues. This short essay focuses on proposing a framework to mitigate liabilities for administering a new formulation on nano-enabled drug carriers particularly when uncertainties of the benefits and damages are not fully known.



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Nano-drug Clinical Trials: Informed Consent and Risk Management Through Blockchain

Yousef Haik* and Ilias Bantekas**

I. INTRODUCTION

Advances in engineered drug bearing nano-capsules have led to an increase in the number of formulations that are being approved for evaluation in clinical trials. Approval of a new drug requires certain experimentation, including on human volunteers to test the efficacy of the new drug formulation. Generally, there are four phases involved in clinical trials. Phase 1 is performed on healthy volunteers to evaluate possible risks of the new drug formulation. In phases 2 to 4, the tests are conducted on patients to evaluate possible therapeutic effect and ultimately confirm said effect and the drug's market approval, respectively. All relevant risks are identified through the four-phase testing process.¹ The number of participants in the evaluation process increases in proportion to the number of new drugs and drug formulations that require approvals. Participants from developed countries are cautious of volunteering for new drugs, particularly those with known high risks or those with a high degree of uncertainty.² The degree of uncertainties in the risk assessment impacts the degree of information provided to participants in the clinical trials.

Clinical trials of a new drug formulation are defined as the series of studies to evaluate the risks, efficacy and the pharmacokinetics³ of the new formulation as compared to a currently used formulation. Both healthy and diseased volunteers are recruited to evaluate the prospective nature of the new formulation. Clinical trials

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¹ The risks of clinical trial participation extend beyond the treatment risks for example issues of privacy and confidentiality of the data obtained during the trial, which is not addressed in this short essay.

² James Cekola, *Outsourcing Drug Investigations to India: A Comment on U.S., Indian and International Regulations of Clinical Trials in Cross-Border Pharmaceutical Research*, 28 NW. J. INT'L L. & BUS. 125 (2007).

³ Pharmacokinetics parameters include absorption, distribution, metabolism, and excretion.

comprise of four phases that describe the stage of development of the drug as well as on the post-marketing authorization.⁴

A recent trend has emerged involving the outsourcing of clinical trials in locations outside the home state of large multinational pharmaceutical companies, most notably in Brazil, China, India, the Middle East or Eastern Europe.⁵ It is estimated that more than 50% of all clinical trials are conducted outside the producers' country of incorporation or headquarters.⁶ The U.S. Federal Drug Administration (FDA) approved over forty formulations of drugs⁷ that employ nanotechnology either in making the active ingredient (e.g. sirolimus⁸) or encapsulating the active ingredient with a protective shell to improve the efficacy and reduce side effects (e.g. liposomal formulation of doxorubicin).⁹ The nano-enabled products that are approved by the FDA receive wide international recognition and acceptance. For example, only 49% of Doxil[®], known internationally as Caelyx[®], and its family of similar products are sold in the U.S. market.¹⁰ Today, there are ten clinical trials that are utilizing Doxil[®] in Saudi Arabia alone.¹¹ Cross border clinical trials are often viewed by volunteers as access to medical treatment that is otherwise unavailable in their home states. Patient

⁴ E.B. Souto et al., *Nanopharmaceutics: Part 1—Clinical Trials Legislation and Good Manufacturing Practices (GMP) of Nanotherapeutics in the E.U.*, 12 PHARMACEUTICS 146 (2020).

⁵ Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816 (2009).

⁶ Wesmos Foundation, *The Clinical Trials Industry in South Africa: Ethics Rules and Realities*, WESMOS FOUND. (July 2013), https://www.wemos.nl/wp-content/uploads/2016/06/Clinical_Trials_Industry_South_Africa_2013.pdf.

⁷ C. Lee Ventola, *Progress in Nanomedicine: Approved and Investigational Nanodrugs*, 42 P&T 742 (Dec. 2017).

⁸ Sirolimus is a target of the rapamycin inhibitor with immunosuppressive properties. Its clinical application is limited due to its poor solubility. The FDA approved the nano-formulation of the drug and is marketed as Rapamune. Liposomal Doxorubicin Market Analysis By Product (J&J [Doxil/Caelyx], Sun Pharma [Lipodox], Teva [Myocet], Others), By Application (Multiple Myeloma, Kaposi Sarcoma, Ovarian, Breast, Kidney Cancer), And Segment Forecasts, 2018–2024, Grand View Research (2016), <https://www.grandviewresearch.com/industry-analysis/liposomal-doxorubicin-market> (Sirolimus is a target of the rapamycin inhibitor with immunosuppressive properties. Its clinical application is limited due to its poor solubility. The FDA approved the nano-formulation of the drug and is marketed as Rapamune.).

⁹ *Id.* (Doxorubicin is an anti-cancer drug that is widely used for the treatment of numerous tumors, including breast, ovarian and lung. However, due to its irreversible cardiotoxicity a liposomal shell was designed to protect the untreated tissue and organs from its toxicity. The FDA-approved liposomal Doxorubicin products are Doxil, Lipodox, and Myoce.).

¹⁰ Grand View Research, *Liposomal Doxorubicin Market Analysis by Product*, GRAND VIEW RES. (Jan. 2016), <https://www.grandviewresearch.com/industry-analysis/liposomal-doxorubicin-market>.

¹¹ See NIH U.S. National Library of Medicine, *ClinicalTrials.gov*, NIH U.S. NAT'L LIBR. MED., <https://clinicaltrials.gov/> (last visited Feb. 7, 2021).

volunteers are less likely to question the treatment procedure or the medication provided to them at no cost.¹²

International law, such as the 1966 International Covenant on Economic, Social and Cultural Rights (ICESCR), guarantees the right of all persons to enjoy physical and mental health. Article 12(1) of the ICESCR provides a “right of everyone to the highest attainable standard of physical and mental health.”¹³ It is evident that the Covenant does not articulate a right to be healthy, which cannot be guaranteed even by the best possible medical attention.¹⁴ Rather, it recognizes the right to enjoy high standards of health, which represents a proposition that is largely dependent on a series of positive obligations. These obligations are of a twofold nature: on the one hand they require the provision of adequate health care services, while on the other they oblige the authorities to satisfy the underlying determinants of health, including basic shelter, food, water, sanitation, safe working environment, freedom from pollution, disease prevention and others.¹⁵ This definition of the right to health, with its two corresponding components, is broader than the definition of “health” in the preamble to the Constitution of the World Health Organization (WHO), which defines health as a “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”¹⁶

The Committee of Economic, Social and Cultural Rights’ (CESCR) General Comment 14 on Article 12 of the ICESCR states that the right to health “includes the right to be free from non-consensual medical treatment and experimentation.” Informed consent in clinical trials has been regulated since 1945, particularly in the

¹² Samiran Nundy & Chandra M. Gulhati, *A New Colonialism?—Conducting Clinical Trials in India*, 352 NEW ENG. J. MED. 1633, 1633 (2005).

¹³ See also U.N. International Convention on the Elimination of All Forms of Racial Discrimination, art. 5 (Dec. 21, 1965), <https://www.ohchr.org/en/professionalinterest/pages/cedr.aspx>; U.N. Convention on the Elimination of All Forms of Discrimination against Women, art. 12 (Sept. 3, 1981), <https://www.ohchr.org/documents/professionalinterest/cedaw.pdf>; U.N. Convention on the Rights of the Child, art. 24 (Nov. 20, 1989), <https://www.ohchr.org/EN/ProfessionalInterest/Pages/CRC.aspx>; Organization of American States Dep’t of Int’l Law, Additional Protocol to the American Convention on Human Rights in the Area of Economic, *Social and Cultural Rights* “Protocol of San Salvador,” art. 10 (Nov. 17, 1988), <https://www.oas.org/juridico/english/treaties/a-52.html>; African Commission on Human and Peoples’ Rights, *African Charter on Human and Peoples’ Rights*, art. 16 (June 27, 1981), <https://www.achpr.org/legalinstruments/detail?id=49>; Council of Europe, *European Social Charter (Revised)*, art. 11 (1996), <https://rm.coe.int/168007cf93>.

¹⁴ Office of the High Commissioner for Human Rights, *CESCR General Comment No. 14: The Right to the Highest Attainable Standard of Health*, ¶¶ 8–9, U.N. Doc. E/C.12/2000/4 (Aug. 11, 2000).

¹⁵ *Id.* ¶ 11.

¹⁶ *Id.* ¶ 4 (The difference here is justified by the fact that the WHO definition focuses on structural factors (system), whereas the right to health is centered on individual health.).

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aftermath of Nazi-led experiments on prisoners and detained persons.¹⁷ Infringement of informed consent has been reported in clinical trials conducted outside the U.S. and the E.U.¹⁸ In these cases, volunteers were either denied crucial information about the phase of testing, the dangers associated with the particular drug, or the company otherwise failed to alert the volunteer to all available data in a way that made sense to the volunteer's level of education, in conjunction with his or her particular financial needs and expectations.

As a result, subsequent (to the trials) claims alleging lack of informed consent have not been infrequent. From the perspective of the claimants, forum shopping is important because of the lack of available, or adequate, remedies in some jurisdictions. The term informed consent first appeared in the writing of the Appellate Court in California, where the court stated that:

A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment In discussing the element of risks a certain amount of discretion must be employed consistent with the full disclosure of facts necessary to informed consent.¹⁹

Claims may be advanced at the producer's home state or their place of headquarters, as was the case with suits against the producers of the Torvan drug,²⁰ even though the clinical trial in question (from which the suit arose) was conducted in Nigeria.²¹ That courts in developed states apply (or not) the *forum non conveniens* principle in order to assert jurisdiction over conduct committed in the (outsourced) country where a clinical trial took place, is an integral part of the notion that multinational corporations (MNCs) are responsible for their direct impact on people and communities in their countries of operation,²² so long as they had a directing role in

¹⁷ See Nuremberg Code, art. 1, Trials of War Criminals before Nuremberg Military Tribunals under Control Council Law No. 10: Nuremberg, Oct. 1946-Apr. 1949, <https://research.wayne.edu/irb/pdf/2-2-the-nuremberg-code.pdf>.

¹⁸ C. Terwindt, *Health Rights Litigation Pushes for Accountability in Clinical Trials in India*, 16 HEALTH & HUM. RTS. J. 84 (2014).

¹⁹ *Salgo v. Leland Stanford Bd. of Trustees*, 154 Cal. App. 2d 560 (Cal. Ct. App. 1957).

²⁰ Trovan is a drug produced by Pfizer, which was found to result in long-term brain damage and death for some of the participants. See *Abdullahi v. Pfizer, Inc.*, 562 F.3d 163 (2d Cir. 2009).

²¹ *Id.*

²² See, e.g., *Chandler v. Cape PLC* [2012] EWC. Civ 525; see *Jabir v. KiK Textilien und Non-Food GmbH* 7 O 95/15 decision of 10 Jan. 2019: "Landgericht Dortmund weist Klage gegen KIK wegen Verjährung ab" (Landgericht Dortmund Pressemitteilung 10.1.19), <http://www.lg-dortmund.nrw.de/behoerde/presse/Pressemitteilungen/PM-Urteil-KIK.pdf>. See V. Grosswald-Curran, 'Harmonizing

the conduct in question,²³ which is usually difficult to ascertain and prove. In regards to claims alleging lack of informed consent in overseas clinical trials, U.S. courts distinguish situations where lack of consent may be treated as a battery claim not requiring injury,²⁴ from situations where lack of informed consent is best treated as a form of negligence, requiring causation and actual injury.²⁵

The legal obligation/liability towards volunteers of a clinical trial depends on the role of the particular “actor” concerned in the various phases of administration of the drug and interaction with volunteers. There are many actors in a clinical trial of a new drug, including the drug-producing company, the researcher(s) or research organizations conducting the trial (which may be a public or private academic institution or a private organization), public or private hospitals, as well as healthcare providers.

The administration of nano-enabled drugs is governed by policies and laws specific to the jurisdiction in which the clinical trials are performed. Informed consent obligations conferred on the investigator in a clinical trial are well entrenched.²⁶ However, there is no internationally recognized risk governance framework for informed consent whereby participants can critically review and agree to its terms ahead of volunteering to the treatment. Jurisdictions that are not fully equipped with sufficient scientific know-how concerning the formulation of nano-drug carriers lack the expertise to assess the risks associated with the complexity, uncertainty and ambiguous nature arising from the administration of nano-drugs. Further, there is no international regulatory framework for admitting nano-enabled drugs to the clinical trial markets.

This Article proposes a risk governance approach for managing associated risks and contributing to informed consent of clinical trials of nano-enabled drugs at the international levels and across national borders. One of the desired consequences of a risk governance framework is an informed consent framework that can provide necessary accountability to manage international clinical trials across borders to a

Multinational Parent Company Liability for Foreign Subsidiary Human Rights Violations, 17 CHI. J. INT'L L. 403 (2016).

²³ See *Okpabi and others v. Royal Dutch Shell Plc* (n.49), upholding, Fraser J. [2017] EWHC 89 (TCC), Sir Geoffrey Vos, Simon L.J., Sales L.J. dissenting; *AAA & Others v. Unilever PLC and Unilever Tea Kenya Limited* [2018] EWCA Civ. 1532.

²⁴ See, e.g., *Canterbury v. Spence*, 464 F.2d 772, 790 (D.C. Cir. 1972) (holding that “[a]n unrevealed risk that should have been made known must materialize, for otherwise the omission, however unpardonable, is legally without consequences”).

²⁵ See, e.g., *Stewart v. Cleveland Clinic Found.*, 736 N.E.2d 491, 501 (Ohio Ct. App. 1999) (holding that “[t]he unrevealed risks and dangers, which should have been disclosed by physician actually materialize and are the proximate cause of the injury to the patient”).

²⁶ S.B. Lee, *Informed Consent: Enforcing Pharmaceutical Companies’ Obligations Abroad*, 12 HEALTH & HUM. RTS. J. 15 (2010).

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diverse set of regulatory frameworks. The article starts with a brief background of nano-drug carriers, followed with a discussion on the risk governance framework and a proposed blockchain for the management of an international risk governance framework of clinical trials.

II. NANO-ENABLED DRUG CARRIERS

The conventional toxic drug, e.g. chemotherapeutics, causes serious, sometimes lethal toxicity due to its off-target effects. Nanodrug delivery offers a novel solution as targeted, drug bearing shells provide site-specific therapy, release the drug and provide on-time remote monitoring. Targeting the diseased tissue with a drug nano-carrier minimizes the side effects associated with toxic drugs by directly carrying the payload to the diseased tissue and releasing it in a controlled and sustained manner. The minimization of side effects is achieved by three functions of the drug nano-carriers, namely: (1) the shells of the nano-carriers are made of material that has an acceptable safety profile, for example, liposomes composed of lipid bilayers with an inner void to entrap the drug; (2) the outer surface of the shells of the nan-carriers are decorated with antibodies or other ligands that adhere to specific surface proteins that are over expressed on cells of the diseased tissue, thus specific targeting against diseased tissue is achieved, which ultimately saves the normal tissue from being exposed to the toxic drug carried in the nano-carrier; (3) the amount of drug encapsulated in the nano-carrier is gauged to a therapeutic dose suitable to treat the diseased tissue as opposed to untargeted drug delivery schemes that require a higher dose circulating through the body with only a small fraction reaching the diseased tissue while the remainder of the circulating drug is negatively affecting normal tissue. Thus, with targeting therapeutic strategies, a smaller amount of drug is deployed, in a way that is designed to reach diseased tissue and engulfed with a biocompatible shell to protect normal tissue from being exposed to the toxic drug.

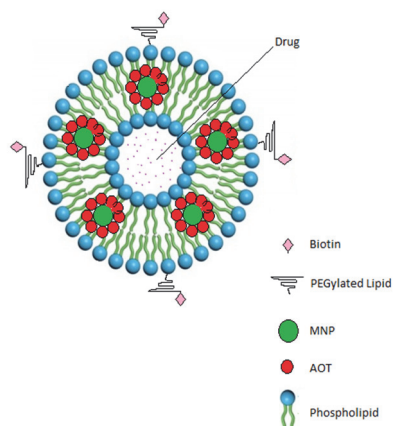


Figure 1: Schematic of a typical thermosensitive targeted drug delivery nano-capsule. It consists of drug in the inner void protected by a lipid bilayer liposome, and decorated with PEG layer to functionalize the carrier for targeted drug delivery. A metallic particle to provide excitation to release the drug on demand.

The FDA approved different formulations of nano-enabled cancer drug delivery carriers based on a liposome shell and doxorubicin, anticancer agent, incorporated in the core of the liposomes to address the limitation of conventional therapeutic delivery systems, including the limitation to deliver the therapeutic drug in concentration to target tissue or the severe toxicity on normal tissue.²⁷ Figure 1 illustrates a typical composition of a nano-enabled drug delivery system that consists of a liposome shell (liposomes are lipid bilayers) enabled with a polymeric lipid for further functionalization to achieve targeted delivery.

The effectiveness of a drug delivery system depends, to name just a few parameters, on the structural properties of the drug carrier, its stability, its interaction with the immune system, residence time in the bloodstream, clinical pharmacokinetics profile, the spatial distribution of the drug shell into different organs, localization into the tumor site, lack of well-defined surface receptors on diseased tissue and the carrier's drug release mechanism. The optimization of all of

²⁷ Alberto Gabizon et al., *Improved Therapeutic Activity of Folate-Targeted Liposomal Doxorubicin in Folate Receptor-Expressing Tumor Models*, 66 *CANCER CHEMOTHERAPY PHARMACOLOGY* 43 (2010).

these constraints is a difficult process and requires a significant amount of research activity in order to address challenges faced in clinical settings. While the optimization of these parameters is still an ongoing research, a number of formulations have been approved for clinical use.

By way of illustration,²⁸ Doxil and Myocet were first approved by the FDA for cancer treatment with a polymeric coating (Poly Ethylene Glycol (PEG)). Doxil has a size of 100 nanometers (nm).²⁹ Both liposome formulations have longer circulation time than free doxorubicin. The longer circulation time results in a larger accumulation of the formulated drug at the diseased tissue. As the size of the liposome decreases the circulation time also increases. Both Doxil and Myocet carry doxorubicin in their liposome shells, they had a better safety profile compared to free doxorubicin, thus underscoring the advantage of the liposome shielding. Lipo-dox was prepared with another PEG-lated liposome formulation that resulted in a circulation time of sixty-five hours. It was observed that the prolonged circulation time resulted in a higher incidence of severe stomatitis compared to the effects of Doxil. It was expected that prolonged circulation time would complement the passive targeting effect and enhance drug uptake at the tumor site. Passive targeting depends on enhanced permeability and retention (EPR) due to the physiological structure of the tumor that results in high tumor uptake compared to normal tissue uptake of drug concentration. The drug diffuses into the tumor cells as a free drug. The rate-limiting step for drug delivery is the release of the drug from the liposomes. In order to address the release of a drug using a stimulus, thermo-sensitive liposomes have been introduced. An example of thermo-sensitive liposomes is ThermoDox, designed to release the drug at 42°C. It was found that there is not much difference in the accumulation of doxorubicin in tumor between Doxil and ThermoDox.³⁰

III. RISKS OF NANO-ENABLED DRUG CARRIERS

Drug containing nano-carriers have emerged as a potential replacement to circulating toxic drugs. The primary aim of shielding a toxic drug with a biocompatible shell is to enhance the therapeutic index of the drugs by increasing its efficacy or reducing its toxicity. Nano-drug carriers shield normal tissue from

²⁸ We are focusing only on a limited number of doxorubicin carriers as an illustration of the complexities and challenges of existing systems.

²⁹ A nanometer is 1 billionth of a meter. To illustrate, an average diameter of a human hair is about 60,000 nanometers and a human DNA is about 2–10 nm wide. Doxil has a circulation time of 55 hours, compared to Myocet that has a size of 190 nm, and a circulation time of just under 2.5 hours. Free doxorubicin has 0.2 hours of circulation time.

³⁰ Alberto Gabizon et al., *Reduced Toxicity and Superior Therapeutic Activity of a Mitomycin C Lipid-Based Prodrug Incorporated in Pegylated Liposomes*, 12 CLINICAL CANCER RES. 1913 (2006).

potential toxicity of harmful therapeutics, thus reducing potential side effects, as well as further decreasing the therapeutic effective dose by virtue of reducing the content drug content within the shell. These nano-carriers are intended to deliver the drug by a myriad of mechanisms, including solubilization, passive targeting, active targeting and external stimulus release.³¹ The encapsulation of drugs with limited aqueous solubility provides a protective environment through which to make it available upon demand.³² The active targeting and external stimulus-controlled release has been reported to enhance the therapeutic index of drugs.³³

Despite the substantial therapeutic benefits of nano-drug carriers, a number of critical challenges and risks have risen during clinical translation. The majority of approved nano-enabled drug carriers incorporate already approved drugs and are based on different shell material, including liposomes, dendrimers and biocompatible polymers.³⁴ Nano-drug carrier technology is by far more complex in comparison to conventional drug formulations that are administered orally or by injection. The nano-enabled drug carriers, due to its complex formulation, have a drug release profile that is different than that of the free drug, which influences the bioavailability of the drug at the diseased tissue. Thus, clinical trials employing nano-carriers are characterized by an unknown degree of efficacy, tolerability and safety, thus posing uncertain and ambiguous risk assessment. The uncertain nature of new drug loaded in nano-carriers poses potential risks for volunteer participants, which is in part a component of the clinical trials' purpose. However, a deeper content analysis is needed to communicate potential risks to clinical trial participants. In the following the key risks and uncertainties, to name a few, associated with nano-carriers are discussed.

A. *Nanotoxicity*

Due to the small size of the nano-enabled drugs, their complex formulation and unknown disposition in biological systems, additional toxicity challenges are considered in addition to those of the drug it carries. A large body of data indicates

³¹ Susan Hua et al., *Current Trends and Challenges in the Clinical Translation of Nanoparticulate Nanomedicines: Pathways for Translational Development and Commercialization*, 9 FRONTIERS IN PHARMACOLOGY 790 (2018).

³² Mikael Larsson et al., *Local Co-Administration of Gene-Silencing RNA and Drugs in Cancer Therapy: State-of-the-Art and Therapeutic Potential*, 55 CANCER TREATMENT REVS. 128 (2017).

³³ Susan Hua et al., *Advances in Oral Nano-Delivery Systems for Colon Targeted Drug Delivery in Inflammatory Bowel Disease: Selective Targeting to Diseased Versus Healthy Tissue*, 11 NANOMEDICINE 1117 (2015).

³⁴ Shashank Chatuverdi, Anuj Garg & Anurag Verma, *Nano Lipid-Based Carriers for Lymphatic Voyage of Anti-Cancer Drugs: An Insight Into the In-Vitro, Ex-Vivo, In-Situ and In-Vivo Study Models*, 59 J. DRUG DELIVERY SCI. & TECH. 101, 899 (2020).

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that reducing the size of a nano-drug carrier significantly increases its circulatory time in the human body.³⁵ The increase in circulation time has two effects: on the one hand it allows for higher accumulation of the nano-carriers on the site of the diseased tissue, while at the same time it increases the likelihood of crossing biological barriers and accumulating vital organs, thus increasing non-selective toxicity.³⁶

B. Biocompatibility

The interaction of nano-carriers with the immune system and the diseased tissue environment affects its therapeutic performance.³⁷ Pre-clinical evaluation of nano-carriers rely on testing the formulations in immune deficient animal models that is projected to provide permissive environment of cross-species' tissue grafting. However, these animal model predictions of how a human patient's immune system will interact with the formulation do not provide accurate predictive assessments.³⁸ For example, PEG-lated nano-carriers that have been widely used in cancer treatment showed that patients treated with these nano-carriers develop antibodies that recognize PEG-lated nano-carriers. Treating patients who develop anti-PEG resulted in accelerated blood clearance, low drug efficacy, hypersensitivity, and, in some cases, life-threatening side effects. Antibodies could be developed not only as a result of administering nano-carriers, but also if patients and volunteers have been exposed to the composition of the nano-carrier by consuming other products that may contain the immunogenic element.³⁹ Immunogenicity of new formulations of nano-carriers could develop life-threatening situations to patients and volunteers if proper assessment of their immune response is not properly conducted.

C. Multi-drug Resistance

Drug resistance could be the result of either intrinsic resistance or acquired resistance. In addition to treatment challenges associated with the non-selective drug administration, which harms both diseased and normal tissue, the acquired drug

³⁵ Alberto A. Gabizon et al., *Pros and Cons of the Liposome Platform in Cancer Drug Targeting*, 16 J. LIPOSOME RES. 175 (2006).

³⁶ Jianbo Jia et al., *Crossing Biological Barriers by Engineered Nanoparticles*, 33 CHEMICAL RES. IN TOXICOLOGY 1055 (2020).

³⁷ Elvin Blanco et al., *Principles of Nanoparticle Design for Overcoming Biological Barriers to Drug Delivery*, 33 NATURE BIOTECHNOLOGY 941 (2015).

³⁸ Stefan Wilhelm et al., *Analysis of Nanoparticle Delivery to Tumors*, 1 NATURE REV. MATERIALS 1 (2016).

³⁹ Thai Thanh Hoang Thi et al., *The Importance of Poly(ethylene glycol) Alternatives for Overcoming PEG Immunogenicity in Drug Delivery and Bioconjugation*, 12 POLYMERS 298 (2020).

resistance has resulted in multi-drug resistance.⁴⁰ The majority of clinically approved nano-carriers are loaded with approved drugs. Thus, the encapsulation with a nano-shell does not address the drug resistance concern. On the contrary, administration of nano-carriers may cause an increase in multi-drug resistance due to the upregulation of drug at diseased tissue.⁴¹

D. Heterogeneity of the Disease in Humans

A high interpersonal variability in the way diseases manifest themselves and, in the way they are treated has been recently recognized as a field of personalized or precision medicine. It is believed that the genetic nature of each human being plays a vital role in how the human body reacts to abnormal conditions and how it reacts to treatment. Relevant to the discussion here, nano-enabled drug accumulation in tumors was reported to vary between tumor types and between patients. For example, liposome accumulation in patient biopsies obtained from breast tumors was $5\pm 3\%$ and from head and neck cancer amounted to $33\pm 16\%$ of the injected dose.⁴² Furthermore, tumors in the same organ may have a different mutation, for example, non-small cell lung carcinoma (NSCLC) accounts for about 87% of all lung cancer, the leading cause of cancer-related death for men and women with an overall five-year survival rate of 10-15%.⁴³ The majority of patients are diagnosed in an advance stage. Efforts to improve the survival of lung cancer patients are currently focused on the development of new target-based therapies that employ nano-carriers.⁴⁴ A successful example of this approach has been the development of therapies targeting the epidermal growth factor receptor (EGFR) in NSCLC.⁴⁵ Patients with EGFR activating mutations (which account for about 10–15% of NSCLC) receive tremendous benefit from EGFR tyrosine kinase inhibitor therapy and have longer

⁴⁰ Ankita Dadwal et al., *Nanoparticles as Carriers for Drug Delivery in Cancer*, 46 ARTIFICIAL CELLS, NANOMEDICINE & BIOTECHNOLOGY 295 (2018).

⁴¹ Alessandro Dalpiaz et al., *Cancer Stem Cells and Nanomedicine: New Opportunities to Combat Multidrug Resistance?*, 25 DRUG DISCOVERY TODAY 1651 (2020).

⁴² Kevin J. Harrington et al., *Effective Targeting of Solid Tumors in Patients with Locally Advanced Cancers by Radiolabeled Pegylated Liposomes*, 7 CLINICAL CANCER RES. 243 (2001).

⁴³ Patrick J. Roberts et al., *Personalized Medicine in Non-Small-Cell Lung Cancer: Is KRAS a Useful Marker in Selecting Patients for Epidermal Growth Factor Receptor-Targeted Therapy?*, 28 J. CLINICAL ONCOLOGY 4769 (2010).

⁴⁴ Rebecca S. Heist et al., *Genetic Changes in Squamous Cell Lung Cancer: A Review*, 7 J. THORACIC ONCOLOGY 924 (2012).

⁴⁵ Cesare Gridelli et al., *Erlotinib in Non-Small Cell Lung Cancer Treatment: Current Status and Future Development*, 12 THE ONCOLOGIST 840 (2007).

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survival time following treatment.⁴⁶ Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (occurring in approximately 15–30% of NSCLC) have been found not to respond to these inhibitors.⁴⁷ This data suggests that nano-carriers need to have proper decoration in their surface for targeting diseases and specific drugs for treating the diseased tissue in the same organ, with a view to offering appropriate treatment for the various subtypes of NSCLC.

The variability in the diseased tissue receptor expressions among patients and among the same type of diseases and, more importunately, patients whose disease tissue lacks well-defined cell surface receptors will not benefit from the nano-carriers' targeted strategy. Volunteers recruited to either evaluate the toxicity of the nano-formulation or its efficacy require in-depth assessment as to their suitability to enroll in the clinical trials. Detailed informed consent is vitally important to outline the potential risks associated with the personalized condition of the volunteer/patient.

IV. OBLIGATIONS AND LIABILITIES IN TRANSNATIONAL CLINICAL TRIALS

A surge in the number of transnational clinical trials for nano-enabled drug carriers is reported.⁴⁸ International clinical trials of nano-enabled drugs may provide a benefit to volunteers and governments in the developing world as it provides access to medical treatment that would otherwise be unavailable and at the same time it saves cost for the producer. The cost of clinical trials in developed countries is almost 90% cheaper than that in developing countries.⁴⁹ However, the delegation to third parties to conduct such trials does not release the manufacturer from its own

⁴⁶ Ariel Lopez-Chavez & Giuseppe Giaccone, *Targeted Therapies: Importance of Patient Selection for EGFR TKIs in Lung Cancer*, 7 NATURE REV. CLINICAL ONCOLOGY 360 (2010).

⁴⁷ Nagahiro Saijo, *Tyrosine-Kinase Inhibitors-New Standard for NSCLC Therapy*, 7 NATURE REVIEWS: CLINICAL ONCOLOGY 618 (2010).

⁴⁸ See U.S. National Library of Medicine, <https://clinicaltrials.gov/> (last visited Oct. 14, 2020) (United States website search of 'nano' revealed 329 studies of nano-enabled products being experimented with 99 trials in Europe, 81 in the U.S., 34 in the Middle East, 28 in East Asia, 26 in Africa, 13 in South America, 9 in Australia, 12 in Canada, 5 in Japan, 5 in Russia, 2 in India and 2 in Mexico).

⁴⁹ Joanne Nicholas, *Outsourcing Clinic Trials*, 104 J. NAT'L CANCER INST. 1043 (2012) (discussing the costs of clinical trials in the United States and China).

liability.⁵⁰ International medical professional organizations⁵¹ require that informed consent be properly obtained and adequate monitoring systems be implemented for all clinical trials. Trial managers are obliged to properly obtain informed consent from volunteers, which itself may be found as far back as Article I of the Nuremberg Code, stating that: “[t]he duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.”⁵² Ethical failures involving experiments with human beings have led to commissions of inquiry and reports that have shaped legal developments in the drugs and research community. In the U.S., for example, the Belmont Report, issued in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, came up with three principles that should underlie all experimental interaction with human subjects, namely: respect for persons, beneficence, and justice.⁵³ The Belmont Report was subsequently instrumental in the creation of the 1991 Federal Policy for the Protection of Human Subjects, otherwise known as the “Common Rule,” which was codified in separate regulations by at least fifteen federal departments and agencies.⁵⁴ The Common Rule outlines the basic provisions concerning informed consent⁵⁵ and assurances of compliance. Section 50.20 of Title 21 of the Code of Federal Regulations (CFR) makes it clear that consent shall only be sought “under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”

The outsourcing of clinical trials in developing countries has led to a string of cases where volunteers questioned the propriety of informed consent. In a case heard

⁵⁰ See General Requirements of Informed Consent, 21 C.F.R. § 50.20 (2020) (emphasizing that “No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.”).

⁵¹ See, for example, European Medicines Agency, Guidelines for Good Clinical Practice E6(R2) (Dec. 1, 2016), https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf, and World Medical Association, Declaration of Helsinki, <https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/>.

⁵² See Nuremberg Code art. 1, Aug. 9, 1947, <https://history.nih.gov/display/history/Nuremberg+Code>.

⁵³ DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, THE BELMONT REPORT (1979), <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html>.

⁵⁴ HHS Protection of Human Subjects Rule, 45 C.F.R. § 46 (2021).

⁵⁵ General Requirements for Informed Consent, 45 C.F.R. § 46.116(h) (2021).

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in Argentina, the judge rejected GlaxoSmithKline's defense that complying with informed consent requirements was a mere formality, the absence of which did not pose an actual risk to the volunteer participants. The court went on to explain that: "even minor deficiencies in the procedure could become relevant later on as certain health effects may only occur in the future."⁵⁶ Drug manufacturers, whether sponsoring international clinical trials or not, have legal obligations arising from such processes has been made abundantly clear. The Indian Supreme Court reasoned that manufacturers have a duty of care towards clinical trial volunteers in accordance with the Caparo test of foreseeability, proximity and fairness.⁵⁷

One of the legal side effects of transnational clinical trial outsourcing is the presumption that informed consent is at best a non-conductive (i.e. not an essential condition for the volunteer/offeree) contractual term, or a tort, assuming that some harm occurs. In the first case the breach of contract arising from the absence of appropriate informed consent does not lead to significant damages and is not a cause for the termination of contract. On the other hand, tort-based liability will arise where local laws require a duty of care (i.e. concerning informed consent) and harm is caused to the participant. It is clear that both contractual and tort-based mechanisms, although useful, should only be used residually and not as the primary source of obligations by drug manufacturers. Human rights laws, as reflected in international human rights treaties and the jurisprudence of international courts and tribunals, should constitute the primary platform for obligations. The current body of international human rights laws clearly suggest that the lack of informed consent constitutes a human rights violation. By way of illustration, Article 7 of the International Covenant on Civil and Political Rights (ICCPR) states that: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."⁵⁸ Article 12 of the ICESCR guarantees the enjoyment of the highest attainable standard of physical and mental health.⁵⁹ General Comment 14 of the CESCR has indirectly linked the right to health with healthcare services provided by private corporations, which typically arise in situations where

⁵⁶ Andrea Gerlin, *Glaxo to Appeal Fines in Argentina Case Over Synflorix Trial*, BLOOMBERG BUS. (Jan. 3, 2012, 3:54 PM), <https://www.bloomberg.com/news/articles/2012-01-03/glaxo-to-appeal-fines-in-argentina-case-over-synflorix-trial>.

⁵⁷ Karine Morin, *The Standard of Disclosure in Human Subject Experimentation*, 19 J. LEGAL MED. 157 (1998).

⁵⁸ International Covenant on Civil and Political Rights art. 7, Dec. 16, 1966, 999 U.N.T.S. 171.

⁵⁹ International Covenant on Economic, Social & Cultural Rights art. 12, Dec. 16, 1966, 993 U.N.T.S. 3.

the State has outsources part of its healthcare obligations private providers.⁶⁰ Although the CESCR did not explicitly refer to clinical trials, it did go on to emphasize that states are under an obligation to regulate “corporations to prevent them from violating the right to health of others.”⁶¹ Given that clinical trials are in their vast majority conducted by private drug manufacturers and that such activities implicate the participants’ and the general public’s right to health, Article 12 CESCR is applicable, in conjunction with the second sentence of Article 7 ICCPR. As a result, both the manufacturer and the host State are under strict obligations to conduct clinical trials in a manner that is human rights-compliant and in addition States must regulate such activities under sanction of law.

A. National Regulation of Nano-Enabled Drug Carrier Trials

The FDA approved formulations of nano-enabled drug carriers through a combination product process that is based primarily on improving the therapeutic benefit with patient survival being equivalent to that resulting from standard treatment.⁶² In the combination product process, a product is categorized and evaluated in accordance with its primary mode of action. For example, the primary mode of action concerning the liposomal formulation of doxorubicin is the chemical action mode. The combination product process allows for the FDA to fast approve formulations that already have a pre-approved primary mode of action in their formulation. The case-by-case approach in conjunction with the combination product process allows the FDA to continue utilizing its regulatory framework and evaluation scheme for nano-enabled products in the same fashion as any other product within its jurisdictions.⁶³ The broad categorization scheme utilized by the FDA may not be suitable to address risks associated with the nano-enabled products due to the potential classification across all three categories. The FDA regulates products under two primary statutes: The Food, Drug and Cosmetic Act⁶⁴ and the Public Health Service Act.⁶⁵ Based on both of these acts, the FDA evaluate products under three broad categories, namely:

⁶⁰ International Covenant on Economic, Social & Cultural Rights cmt. 14, Dec. 16, 1996, 993 U.N.T.S. 3.

⁶¹ See ICCPR, *supra* note 58, ¶¶ 48, 51.

⁶² M.E.R. O’Brien et al., *Reduced Cardiotoxicity and Comparable Efficacy in a Phase III Trial of Pegylated Liposomal Doxorubicin HCl (CAELYXTM/Doxil) versus Conventional Doxorubicin for First-Line Treatment of Metastatic Breast Cancer*, 15 ANNALS ONCOLOGY 440 (2004).

⁶³ Jordan Paradise, *Regulating Nanomedicine at the Food and Drug Administration*, 21 A.M.A. J. ETHICS 347 (2019).

⁶⁴ The Act regulates chemically synthesized drugs as well as devices. See Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 321–399i (2018).

⁶⁵ The Act regulates biologically derived products. See Public Health and Safety Act, 42 U.S.C. §§ 209–291n (2018).

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(1) *Chemical mode of action*. These include any drug that is chemically synthesized and is intended for use in diagnostics, treatment or prevention of a disease.

(2) *Biological source*. These include products that have biological origin or analogous that is intended for the prevention or treatment of human disease.

(3) *Mechanical mode of action*. These are medical devices that are intended for the diagnosis, mitigation, treatment or prevention of a disease.

The combined product process is short of making a full evaluation of the product as it focuses on the primary action mode of the product; hence the unintended effects of nanoparticles that make up the product and its novel mechanism of interaction with the human body may not be fully assessed. The existing regulatory system meets the traditional risk-benefit measures; however, potential adverse effects of a broad range of nanomaterial are not well known and much research is yet to be conducted.⁶⁶

The uncertain nature of new nano-enabled drug carriers poses potential risks for volunteer participants, which is in part a component of the purpose underlying clinical trials. However, the risk of inadequate informed consent is foreseeable and companies, sponsors and investigators can and should be held liable. Even in the absence of injury, the lack of reliable informed consent in itself is wrongful and injurious.⁶⁷ The proximity requirement in establishing the Caparo test is established by all participants in supplying and administering the drug. Under normal conditions, the courts in the United States, have espoused two views concerning the treatment of claims arguing for lack of adequate informed consent, namely: situations where a lack of informed consent would be treated as a battery claim which does not require injury⁶⁸ or as a negligence claim that requires causation and actual injury.⁶⁹ These legal standards are fact-specific and subject to different interpretation. *Shloendorff v. Society of New York Hospital*⁷⁰ established the root premise of true consent, where it

⁶⁶ David B. Resnik, *How Should Engineered Nanomaterials be Regulated for Public and Environmental Health?*, 21(4) A.M.A. J. ETHICS 363 (2019).

⁶⁷ *Lugenbuhl v. Dowling*, 701 So. 2d 447, 455–56 (La. 1997).

⁶⁸ See, e.g., *Canterbury v. Spence*, 464 F.2d 772, 790 (D.C. Cir. 1972) (holding that “[a]n unrevealed risk that should have been made known must materialize, for otherwise the omission, however unpardonable, is legally without consequences”).

⁶⁹ See, e.g., *Stewart v. Cleveland Clinic Found.*, 736 N.E.2d 491, 501 (Ohio Ct. App. 1999) (holding that “[t]he unrevealed risks and dangers, which should have been disclosed by physician actually materialize and are the proximate cause of the injury to the patient”).

⁷⁰ *Schloendorff v. Soc’y of New York Hosp.*, 211 N.Y. 125, 105 N.E. 92, 93 (1914), *abrogated by* *Bing v. Thunig*, 2 N.Y.2d 656, 143 N.E.2d 3 (1957). See also *Natanson v. Kline*, 186 Kan. 393, 350 P.2d 1093, 1104 (1960).

was argued that: “[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body.” True consent is “the informed exercise of a choice, which entails an opportunity to evaluate knowledgeably the options available and risks.”⁷¹ In *Helling v. Carey*⁷² the court held that the health care provider’s compliance with the standards of protection as established by a reasonable prudent professional is necessary to shield him from negligence claim. The average volunteer for evaluating the efficacy of a new nano-carrier has little to no understanding of the uncertainties and risks and only the developer of such drug “may” have the highest possible knowledge of said risks. Thus, for the volunteers to reach an intelligent informed decision they must necessarily rely on the expertise of the developer.

While clearly there is no doubt, at least in the developed world, that drug manufacturers and their agents have a duty of care in the administration of clinical trials (one of the foundations of tort-based liability), it is equally recognized that the proximity of the relationship between the end-user of drugs and the drug producer is limitless. The Federal Court of Australia considered that “by placing on the market a product to be consumed by end-users, the manufacturer of prescription medicine, no less than the manufacturer of any other product intended for human consumption establishes the setting for the creation of the relationship of proximity which the common law duty of care arises.”⁷³ The uncertainty of risks associated with new formulations of drugs that employ nanotechnology does not shield manufacturers, sponsors or investigators from liability. The next section proposes a risk governance approach to help mitigate liabilities that could arise from the uncertainty of risks associated with administering nano-enabled drugs.

V. RISK GOVERNANCE

The emergence of specialized drug-bearing nano-capsules have engendered substantial benefits for providing onsite controlled treatment of diseases that otherwise require a whole-body exposure to toxic drugs. However, nano-enabled drugs present unique challenges for regulators, because the potential risks are broader and more diverse than commonly regulated drugs. The unanticipated vulnerabilities and risks may result in an unfair burden of risks to volunteers in

⁷¹ *Canterbury v. Spence*, 464 F.2d 772, 780 (D.C. Cir. 1972).

⁷² *Helling v. Carey*, 519 P.2d 981 (Wash. 1974), *disapproved of by* *Barton v. Owen*, 139 Cal. Rptr. 494 (Ct. App. 1977).

⁷³ *Peterson v. Merck, Sharpe & Dohme (Aust.) Pty.* (2010) 184 FCR 1 (Austl.).

clinical trials and consumers in a manner that compromises the informed consent and public confidence towards new nano-enabled treatment modalities.

An informed consent that is based on risk governance rather than a risk assessment could provide a more informed risk profile of nano-capsules drug carriers, such that could reduce and possibly mitigate the unanticipated uncertainties in managing volunteer and patient consent. Risk management includes identification, controlling, moderating and communicating complex and ambiguous risks.⁷⁴ Nano-shell bearing drugs pose a complex nanostructure that has a variety of materials in its composition that could attribute to different effects that could be difficult to quantify as one risk. For example, drug carriers may be composed of polymeric and or lipid structures, with and without drug release agents that could involve an inorganic structure, as well as the drug itself. Each of these constituents has its own potential risks and uncertainties and the structure as a whole encompasses a compounding number of risks. Risk governance is composed of five components, which include:⁷⁵

- (1) Risk pre-assessment that focuses on providing potential risks, setting priorities, gathering risk data, developing decision making criteria and mitigation strategies;
- (2) Risk appraisal that combines the scientific risk assessment of the potential health implications and its likelihood to occur with consideration to volunteers and patients concerns and risk perception;
- (3) Evaluation of risk and its tolerability. This evaluation combines evidence from scientific data and judgment based on the potential effect on the quality of life of volunteers and patients;
- (4) Risk management that identifies actions and remedies to eliminate or reduce the risk; and
- (5) Risk communication that allows for volunteers and patients to participate in the governance process.

Risk governance for international clinical trials of a nano-enabled drug can mitigate potential liabilities associated with uncertainties and ambiguities of potential health risks arising from the administered trial drug. The results acquired through international clinical trials have the potential to advance the combating of deadly diseases. Risk governance would allow for transnational regulatory

⁷⁴ L. Trevena, *Assessing Communicating and Managing Risk in General Practice*, 64 BRIT. J. GEN. PRAC. 166 (2014).

⁷⁵ Peter D. Jacobson, Sarah J. McHugh & Valerie K. Tran, *Risk Governance and Population Health*, 53 JURIMETRICS 279, 283 (2013).

coordination of clinical trials. The regulatory cooperation would be a tool to harmonize and align regulation between producers and host states. The harmonized regulation would not be the minimum nominator but rather an internationally acceptable standard, subject to human rights compliance. The marginal differences in regulation would allow for the cultural social and political differences between jurisdiction and that does not marginalize by any mean risk over benefit.

VI. LIABILITY AND RISK GOVERNANCE

Clinical trials employing nano-enabled drug carriers are characterized by their unknown efficacy, tolerability and safety, thus posing uncertain and ambiguous risk assessment. A deeper content analysis is needed to communicate potential risks to clinical trial participants. Clinical trial-related legislation and its construction by the courts has played a vital role in developing frameworks to communicate risk information to clinical trials participants. Both have extended the legal protection to participants in circumstances where clinical trials are conducted extraterritorial, provided that the sponsor has legal personality under its particular jurisdiction.⁷⁶

A number of potential liabilities could arise out of informed consent for nano-drug related clinical trials, including:⁷⁷

1. *Conflict of interest.* Failure to adequately communicate with the clinical trials participant the extent of one's conflict of interest and the financial dependence of the sponsor associated with the nano-drug being tested could very well constitute the basis for a suit, whether contractual or in tort. In *Wright v. Fred Hutchinson Cancer Center*,⁷⁸ the plaintiffs alleged that their family members were not provided with all the information necessary to understand the proposed treatment, the possible risks and benefits of the research protocols, nor defendants' financial interests in the clinical trials. Publicly-mandated risk governance dictates that any potential conflict of interest be made available to the participants in a clear and direct manner.
2. *Adverse events liability.* Failure to make a complete and accurate representation of the nano-drug carrier's potential risks could give rise to liability. In *Quinn v. Abiomed*⁷⁹ it was alleged that the information provided to the participant was insufficient to properly inform him of the

⁷⁶ See generally 45 C.F.R. § 46.102(e) (2019).

⁷⁷ The authors are not aware of any court case that involve nano-drug carriers and hence the cases referred to here are based on traditional drugs or medical devices.

⁷⁸ *Wright v. Fred Hutchinson Cancer Research Ctr.*, 269 F. Supp. 2d 1286 (W.D. Wash. 2002).

⁷⁹ *Quinn v. Abiomed, Inc.*, No. 001424 (Pa. Ct. Com. Pl. 2002).

ramifications of his decision to participate in the clinical trial. Risk governance requires that scientific risk assessment of potential health implications be communicated in a clear manner to participants. Thus, an active prediction of all certain, potential, as well as uncertain (but possible), risks must be made available to participants.

3. *Efficacy of the nano-drug carriers' liabilities.* Misrepresentation of the efficacy of the experimental nano-drug carriers may give rise to potential liability. The nature of the nano-drug carrier's development is prone to efficacy misrepresentation. The composition and the formulation of the nano-drug carrier may work *in vitro* or in animal studies, but otherwise fail miserably in humans due to differential immune system responses. Thus, high anticipation of efficacy could be baseless when translating the drug from the lab into clinical trials. In *Daum v. Spinecare Med. Group, Inc.*⁸⁰ the plaintiff alleged that he was not informed that the device had not been approved by the FDA. Risk governance requires that uncertain risk be evaluated based on scientific evidence that leads to an informed judgment of the potential efficacy of the administered nano-drug carrier.
4. *Ineffective consent.* Improper, or lack of informed consent is equally a basis for both contractual and tort claims. In *Stewart v. Cleveland Clinic Foundation*⁸¹ the plaintiff alleged that he was not informed of prior studies of combined modalities (chemotherapy and radiation), nor was he informed that he was expected to receive a combined modality treatment. It is inherent in risk governance that the operator identifies actions and remedies to eliminate or reduce the risk and to communicate these risks to allow for volunteers and patients to participate in the governance process.

In the international human rights system, both the producers and the host states of clinical trials bear the duty of care. Risk governance helps both the producer and host states to manage obligations under human rights. The risk governance approach is consistent with the reports of the UN Special Rapporteur on the Right to Health, who emphasized that: "A rights-based approach to medical research means that special protections must be in place to ensure that the autonomy of potential participants, particularly those from vulnerable groups, is not compromised as a

⁸⁰ *Daum v. Spinecare Med. Group, Inc.*, 61 Cal. Rptr. 2d 260 (Cal. Ct. App. 1997).

⁸¹ *Stewart v. Cleveland Clinic Found.*, 736 N.E.2d 491 (Ohio Ct. App. 1999).

result of power imbalances inherent in the research-subject relationships.”⁸² The continuum of translating nano-enabled drug form basic research to clinical trials goes through a diverse range of experimentation. Adaptation of risk governance is viewed as an integral part of quality health care management.

VII. BLOCKCHAIN AND RISK GOVERNANCE REGISTRY

Blockchain is a form of digital information stored in a public database. Blockchain is based on the ledger keeping method that is distributed across many stations, through a peer-to-peer network, which functions on the basis of a cryptographic communication scheme to ensure the security of its records.⁸³ All connected peers hold identical copies of the ledger machine consensus.⁸⁴ While bitcoin (or cryptocurrency) is the most recognized application of blockchain, many other applications are being advanced, particularly in the context of sharing inter-organizational data, digital asset registration or integrity and identity management.⁸⁵ To simplify the concept of blockchain in risk registry of nano-carriers in transnational clinical trials, consider the blockchain of risk registry as a computer file that is stored in a computer in the network, say a location where the clinical trial is being carried out, the file is broadcasted to other locations on the network of transnational clinical trials for risk register sharing and updates. The risk registry generated from one transnational clinical trial location will be shared with all on users (e.g. other locations and regulators of foreign and domestic). The blockchain ensures the integrity and security of the information because it is built on a system of distributed consensus which does not allow changes unless all participants agree to the change.⁸⁶

There are three main categories of blockchains, namely public blockchain where access to join the network is granted to anyone with an intent to join the

⁸² Anand Grover (Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health), *Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health*, U.N. Doc. A/64/272 (Aug. 10, 2009).

⁸³ Alan Cohn et al., *Smart After All: Blockchain, Smart Contracts and Smart Energy Grids*, 1 GEO. L. TECH. REV. 273, 277 (2017).

⁸⁴ Jesse Yli-Huuma et al., *Where Is Current Research on Blockchain Technology?—A Systematic Review* (2016) PLOS ONE (Oct. 3, 2016), <https://doi.org/10.1371/journal.pone.0163477>.

⁸⁵ Muniba Memon et al., *Blockchain Beyond Bitcoin: Blockchain Technology Challenges and Real-World Applications*, INST. ELEC. & ELEC. ENG’RS (2018), <https://ieeexplore.ieee.org/abstract/document/8658518>.

⁸⁶ Christopher Mann & Daniel Loebenberg, *Two-factor authentication for the Bitcoin Protocol*, SPRINGERLINK (Apr. 5, 2016), <https://doi.org/10.1007/s10207-016-0325-1>.

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network. Upon joining, the participant is enabled to add information, approving tasks or make new addition to the ledger.⁸⁷ Private or permissioned blockchain where a new user can only join a network through an invitation scheme that checks whether the new user meets a set of conditions established by the peer-to-peer network. Once access is granted, the new user will be provided with authentication, access control and privileges.⁸⁸ Consortium blockchain is where a semi-decentralized data structure that are controlled by a single organization in the same fashion as that of the permissioned blockchain. This scheme is utilized to manage the growth of the data file that is distributed across the network and act as a consensus system for any new information to the ledger being handled by the network.⁸⁹

The distribution of data from a single database to distributed databases increases decentralized control and storage of records that have the potential to increase the trust and give rise to the collaborative system. By using blockchain, the efficiency of the risk registry system will be increased and result in better synchronization and countering the security issues and availability of information.

Permissioned blockchain recording system provides protective access to include new risk registries from clinical trial conductors from around the globe. It also allows the producers to have a platform to gather all risk data generated from all participants, thus subsequently improve the risk governance which subsequently improves the informed consent. The distributed feature of the blockchain ledger allows for collaborative sharing of risk data by all of those sharing the data in a network consisting of all participants of the outsourced clinical trials. Distributed ledgers allow all clinical trials monitoring personnel (onsite or remotely) within the network to access and visualize changes to the ledger as they occur while maintaining the information safe from unauthorized access via cryptographic keys and signatures.⁹⁰ The technology represents an opportunity for evolution in various fields of clinical trials risk governance given its adaptability to all elements of risk governance. Transparency and disclosure are at the base of good risk governance models in that they enable clinical trials participants to make informed decisions.

Tracking risk governance registry for international clinical trials of nano-enabled drug delivery carriers provides substantial advancement to materializing new treatment regiments around the globe. It allows for robust and standardized

⁸⁷ Nadine Kathrin Ostern, *Blockchain in the IS research discipline: a discussion of terminology and concepts*, SPRINGERLINK (Dec. 20, 2019), <https://doi.org/10.1007/s12525-019-00387-2>.

⁸⁸ Trevor I. Kiviat, *Beyond Bitcoin: Issues in Regulating Blockchain Transactions*, 65 DUKE L.J. 569, 569 (2015).

⁸⁹ Madhavi Latha Nandi et al., *Blockchain Technology-Enabled Supply Chain Systems and Supply Chain Performance: A Resource-Based View*, 25 SUPPLY CHAIN MGMT. 841, 841 (2020).

⁹⁰ Alex Hughes et al., *Beyond Bitcoin: What Blockchain and Distributed Ledger Technologies Means for Firms*, 62 BUS. HORIZONS 273, 273 (2019).

electronic trials data record-keeping that can be inspected by regulators remotely. It allows for the identification of problems at the early stage of the trial. The risk governance registry enables the recruitment of volunteers and at the same time enables regulatory oversight for new drug approvals.

A. Blockchain and Risk Governance of Informed Consent

Clinical trials of the same drug could be running simultaneously at different locations by different conductors. For example, ThermoDox is currently under twelve clinical trials testing efficacy against liver, breast and bone cancer at different locations (United States, United Kingdom, Netherland, China, and Canada).⁹¹ Massive data will be generated out of these clinical trials. Blockchain strategy for risk governance will enable collection of all data and making available globally and on-time.

The blockchain ledger of all five risk governance elements (pre-assessment, appraisal, evaluation and tolerability, management and communication) complies with recent ruling in the United States that requires for all clinical data to be made available to healthcare providers and patients. In *Seife and Lurie v. U.S. Department of Health and Human Services*,⁹² The plaintiff claimed that “The basic reporting requirements deprived them as well as other researchers and advocates, of the data necessary to ensure transparency in research, promote better decision-making by clinicians and policymakers, eliminate bias in the medical literature, and to make patients, clinicians, and regulators aware of medical product safety and effectiveness.” The basic requirement for drug approval under the FDA statues does not require that all data be made available. However, the possibility of producers to only share data that in favor of their product is highly possible, leading to healthcare providers to prescribe drugs that are ineffective or unsafe. Extending this ruling to pre-clinical data that is required for the recruitment of volunteers for clinical trials improves immensely the informed consent practice, particularly for nano-enabled drugs that definitely have higher uncertainty and ambiguity than conventional drugs due to the fact that multiple additional active components are added to the formulation in addition to the already toxic drug.

Risk governance for nano-drugs needs to run in parallel with all stages of nano-drug clinical trials. Blockchain ledgers associated with each element of the risk assessment. A block that consist of index, timestamp, list of risk data entry transactions, proof and a connector to other blocks.

⁹¹ See Search Results for “ThermoDox” and “Cancer” on ClinicalTrials.gov, U.S. National Library of Medicine, <https://clinicaltrials.gov/ct2/results?cond=cancer&term=ThermoDox&cntry=&state=&city=&dist.>

⁹² *Seife et al. v. HHS et al.*, 440 F. Supp. 3d 254 (S.D.N.Y. 2020).

The decentralized standard for transnational clinical trials risk registry allows for the disclosure of registered risks among all participating sites, thus strengthening the components of informed consent and build trust between international pharmaceutical drug producers and the governments where the volunteers are recruited. Further it allows for the regulatory bodies to have access to all relevant data ahead of pre-marketing approval. The benefits of deploying blockchain technology of risk registry of drug nano-carriers could be summarized in the following points:

- **Transparency:** Every node on the network will have a complete documentation of the registered risk and holds history of the registry that can be visible to all permissioned to view anytime and from anywhere. Thus, clinical trials directors at all locations will be able to view the risk and inform potential volunteers or take actions to mitigate risks of currently participating volunteers. It also allows for the regulators and government agents to review the risks as they registered from all participating locations. Thus, facilitating the administration of informed consent even at locations where the risks have not yet been registered.
- **Build trust:** Transnational clinical trials are painted with a dark record of unethical behavior of a number of pharmaceutical key players. Regulatory bodies at different locations may have different requirements to authorize clinical trials in their territories, however, access of immutable risk registry record keeping and verification of data at multiple nodes facilitate trust building between transnational regulators and global pharmaceutical industry.
- **Risk predictability:** The risk history maintained at different nodes and generated from clinical trials at different locations facilitates prediction of risk at new clinical trials locations.
- **Reliability:** The risk registry is stored at multiple nodes through the blockchain system, the consensus scheme assures change of information only when other relevant peers approve. Thus, tampering with risk registry is minimized.
- **Security:** Data are stored at multiple nodes using encryption which will prevent tampering with data without proper authentication.
- **Ease of access:** The availability of data at the distributed nodes on the net enhances the ease and speedy access of risk registry data.

The challenges that may arise of employing blockchain technology to risk governance of clinical trials that involve nano-drugs include:

- IP protection of the technologies, not only the blockchain platform, but also the nano-drug. Volunteers of the clinical trials, particularly those at developing countries, are not concerned with IP infringements. The permission blockchain could mitigate this concern by restricting shared information to only those who are participating in the study and only information pertaining to informed consent.
- Confidentiality of the data, which includes the personal data of the volunteers as well as the research data obtained at the different phases of the trial. A new prescription drug value is backed by the scientific evidence supporting the product. Transparency of data ensures that all positive and negative implications of the nano-drug be made available to volunteers to make an informed decision. Confidentiality of data to sponsor could be managed by blockchain ledger to only allow for participants to view the data. This is probably the most problematic challenge that could face a producer, as it makes all of its data be potentially available to its competitors. However, the producers are legally bound by the informed consent doctrine to make all data available to volunteers so they can make an informed decision. The risk governance will ensure that only products that meet the safety threshold to reach to state of efficacy evaluation with human volunteers.
- Regulatory measures to catch up with the advancement in both the nano-drug technology and that of the blockchain. This essay contends that new regulatory approaches are needed to address nano-drug. Current regulatory measures are based on extrapolation of conventional regulatory instruments to rapidly address known concerns. However, those were developed for technologies that are not viable at the nanoscale. The risk governance provides a systematic approach for designing balanced regulatory measure that on one hand allows for new scientific discovery to progress and on the other mitigate unnecessary exploitation of vulnerable volunteers to unsafe drugs.

The blockchain management of risk governance of nano-drug clinical trials provides a technological tool that increases transparency, mitigates the legal claims associated with informed consent and affirms the legal burden on both producers and host state to ensure that uncertainties and ambiguities are addressed ahead of instituting drugs to volunteers. Further, the approach helps all sites participating in clinical trials to have direct and immediate access to data to manage risks that were discovered at remotes sites.

VIII. CONCLUSION

Informed consent and rigorous monitoring systems are only two vital elements among many that need regulation for the protection of participants of international clinical trials. At the moment there is no internationally recognized regulatory framework for outsourced clinical trials for new nano-enabled drugs. The uncertainty of risks with new drugs requires the establishment of a more rigorous framework for addressing the associated potential adverse effects. A risk governance framework will mitigate the ambiguous risks and provide more informed consent to prenatal participants, which will assist in recruiting informed volunteers and reduce potential liability. A blockchain registry will ensure the availability of data to assist local legislators to only grant the right to clinical trials that could benefit the local population. The registry could create an obligation for post-trial access to treatment.