Chapter 6

**Ethics and Policy for 3D Bioprinting (draft 09.08.19)**

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**i. Summary/Abstract**

3D bioprinting involves engineering live cells into a 3D structure; using a 3D printer to print cells together with a compatible 3D scaffold. 3D printed cells and tissues may be used for a range of purposes including medical research, *in vitro* drug testing and *in vivo* transplant materials. The inclusion of living cells and biomaterials in the 3D printing process raises ethical, policy and regulatory issues at each stage of the bioprinting process that include the source of cells and materials, stability and biocompatibility of cells and materials, disposal of 3D printed materials, intended use and long-term effects. This chapter focuses on the ethical issues that arise from 3D bioprinting in the lab – starting with consideration of the source of cells and materials, ensuring their quality and safety, continuing through to testing of bioprinted materials in animal and human trials. It also provides guidance on where to seek information concerning appropriate regulatory frameworks and guidelines, including on classification and patenting of 3D bioprinted materals, as well as identifying regulatory gaps that deserve attention.

**ii. Key Words**

human research ethics, animal research ethics, governance, regulation, bioethics

**1. Introduction**

3D bioprinting involves the use of 3D printers to engineer live cells into a 3D structure for purposes that include increased understanding of biological processes or conditions and improving patient well-being and health. The addition of living cells within the printing process engenders technical challenges related to cell viability and proliferation – to find biocompatible materials to serve as scaffolds for cells and that protect cells during the printing process while achieving mechanical and functional properties for tissue constructs (1: page 778). The inclusion of living cells within the printing process also raises ethical issues related to the source of the living cells and the intended use of the bioprinted materials, policy issues related to protecting human health and safety and have begun demand for regulatory frameworks to address regulatory challenges, which researchers will need to anticipate and adequately respond to in developing 3D printing techniques and applications.

The typical process for 3D bioprinting of tissue involves three stages: pre-printing, printing and post printing. The pre-printing stage includes: imaging, design approach and selection of scaffold material and cells. The printing stage involves selection of bioprinting method. The post-printing stage focuses on the application of the bioprinted material, including maturation, implantation and in vitro testing (2). In addition to technical challenges, ethical issues arise at each stage of the bioprinting process. The kinds of ethical issues that arise will depend, in part, on the purpose of research being undertaken and the application to which it is put, be it pure research (for example, the study of cell behaviour to understand processes of organisms); development of new human and/or animal models for *in vitro* diagnostics (for example, pharmaceutical testing); or *in vivo* therapeutic applications (for example, the implantation of 3D bioprinted materials). Researchers are moral agents with ethical responsibilities at each stage of research, from the bench to clinical research (3). Attention needs to be paid to research design, including assessment of the purpose and use of the research. Some of these issues are common to other research relevant to clinical care (such as accurate and appropriate recording of methods and findings).

Because of the novelty and breadth of potential applications, 3D bioprinting raises broad ethical questions, akin to other emerging technologies, including questions about justice in access to treatment (4) and the legitimate purposes of 3D bioprinting research, for example, treatment of conditions versus extending or enhancing human function (5). While these broader issues are important, this chapter focusses on ethical and regulatory issues that researchers who make use of 3D bioprinting in the lab will need to take into account**.[[1]](#footnote-1)** Given the ultimate purpose of 3D bioprinting is to advance human health, this chapter starts with a general discussion of the use of humans in research and the importance of research design. The following four sections discuss ethical and policy issues relating to 1) consideration of the source of cells and materials (human, non-human and other), including issues related to donation and consent of human cells; 2) ensuring the quality and safety of cells and materials used in 3D bioprinting; 3) testing the safety and efficacy of 3D bioprinted materials in animals and humans; and 4) classification and patenting of 3D bioprinted tehcnologies. Each sections concludes with a suggested set of questions researchers might ask themselves to assist in orienting themselves toward the ethical, policy and regulatory issues that arise from their research. These sections refer to policy and regulatory frameworks including the United States, Australia, European Union, and United Kingdom). Reference to specific regulation in this chapter is not intended to be exhaustive, rather, it is to indicate the types of issues that may arise and where to look in the regulations to address these.

Researchers should be mindful that there is no single regulatory regime that governs the entire bioprinting process, and that there are different regulatory approaches in different jurisdictions (6: page 441). There is a range of regulations and guidelines or law that may be relevant to the technique and type of research. In part, this arises from the number of techniques that are used in the 3D bioprinting process, as well as the integration of materials from varied biological and synthetic origins in novel ways. Rapid advances in materials science and techniques, and the multiple applications to which 3D bioprinted material is put, challenge regulatory frameworks to keep up (6: page 441). As such, researchers need to attend to multiple forms of regulation, which may relate to the materials and the purpose or application of their research, as well as be mindful of potential regulatory gaps and anticipate ethical issues where there is a lack of clear guidance. As this is an area of rapid regulatory change, researchers should consult regularly with local research governance bodies for updates relevant to their research.

**Questions to consider:**

* What is the purpose of the 3D bioprinting research being undertaken? For example:
  + Establishing a technique
  + Testing the viability of cells
  + Evaluating scaffold materials
  + Developing diagnostic tools
  + Developing therapeutics for use in humans
  + Developing therapeutics for use in animals
  + Animal testing of therapeutics for human use
  + Animal testing of therapeutics for veterinary use
* What is the source of cells used in the research? For example:
  + Non-human embryonic stem cells
  + Human embryonic stem cells
  + Non-human induced pluripotent stem cells (iPSCs)
  + Human iPSCs
  + Autologous stem cells
* Will the 3D bioprinted materials be implanted into a living organism? If so:
  + Will the materials be implanted into the organism from which they derived (autologous)?
  + Will the materials be implanted into a different organism of the same species?
  + Will the materials be implanted into a different species of organism?
  + Will 3D bioprinted materials derived from a non-human species be implanted in a human?
* Have the materials being used as a scaffold for 3D bioprinting been tested and approved for use in humans? For veterinary purpoes?
* Have the scafford materials been tested for biocompatibility?
* If the 3D printed materials are intended for use in a living organism, is the scaffold intended to be biodegradable or enduring? Have they been tested for biodegradability and long term stability; to ensure they do not cause scarring or infection; and are their interactions with other implants or therapeutics known?

A significant proportion of the research being undertaken with 3D bioprinting has as an ultimate aim the development of better diagnostics and therapies for human health. It is invisaged that developments in 3D bioprinting will allow for greater personalisation of treatments by using patients’ own cells to develop highly refined diagnostic tools – a “lab on a chip” – and integrated therapeutics printed into a patient’s stem cells as part of the next phase of regenerative medicine, stem cell therapies and implanted targeted delivery. While there is 3D bioprinting being undertaken that focuses on proof of concept using non-human animal models, it is worth keeping in mind that if the ultimate purpose of a research program is to benefit human health, then that research needs to attend throughout to the ethical and regulatory significance of use of humans in research. This includes the justification of using people as research subjects where they may not be beneficiaries of the research, the ethical and requlatory requirements regarding minimising risk, informed consent, privacy and subsequent use of data from research.

Similarly, 3D bioprinting research involving non-human animals needs to be informed by awareness of the ethical concerns abut the use of animals in research, regulatory requirements regarding use of animals, the mininmisation of pain and suffering, ensuring appropriate stimulation and care and the need to justify use of animals for research purposes. In the case of research involving xenografts (transfer of live cells between different species), there will often be additional regulatory controls to take into consideration.

**2. Using Humans in Research**

Humans may be used as the source of cells in 3D bioprinting (embryonic or adult stems cells) as well as people being involved as participants in research on the effectiveness and reliability of 3D bioprinted diagnostics and in research on the safety, effectiveness and side effects of 3D bioprinted therapies. This means that ethical and regulatory issues may arise around the source of cells, the design and effectiveness of diagnostics, and therapeutic devices or treatments involving 3D bioprinting.The use of lives cells derived from humans in the 3D bioprinting process, including uses with the ultimate purpose of developing clinical treatments, raises ethical issues about the use of humans in research. Human research is research conducted with or about people, or their data or tissue (7, page 3). Research involving humans is an important step in ensuring advances to human health and well-being have a strong empirical basis and ensuring treatments are safe, reliable and effective, but research involving humans can also introduce significant risk of harm to participants in the research. Researchers have an ethical responsibility to minimize risks to participants through good practice with attention to ethical values which protect and respect human participants to ensure that the health, wellbeing and autonomy of individual participants are adequately protected in the conduct of the research (8, page 50).

Each country has developed ethical guidelines or protocols for conducting and evaluating research involving human participants. Many of these guidelines derive in part from the ethical principles set out in the World Medical Associations’ Declaration of Helsinki (9) and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health Related Research Involving Humans (10). Common to these guidelines are ethical principles relating to participant autonomy and informed consent, privacy, minimisation of harm, and justice in the distribution of benefits and burdens of research. In Australia, for example, these are expressed as guiding ethical principles which should inform research: research merit and integrity, justice, beneficence and respect (7). Independent review boards also exist for ethical assessment and approval of proposals for conducting research involving human participants - in the US, Institutional Review Boards (IRBs), in Canada, Research Ethics Boards (REBs) and in Australia, Human Research Ethics Committees (HRECs).

Historically, human research ethics guidelines and research ethics review committees have focussed on the impact of research on human participants and on the groups affected by a particular area of research (for example, social groups or populations sharing a particular condition). Some countries have legislation or guidelines concerning the extraction and use of cell lines derived from humans, some of which would be found in research ethics guidances, but in some countries there would be separate legislation specifically addressing the extraction and use of cells and cell lines which may include information about the control of private information, required information for donors and advice about the agreed use of data derived from donated human cells (see **section 3.a** and **section 4** below). In addition to research ethics guidelines are guidelines about research on the human embryo, clones, chimeras, genetic material and tissues (11, 12), however there is no single approach to regulation and guidelines on research involving human tissues and, as yet, few countries have developed guidelines that specifically address 3D bioprinting of human cells or the use of 3D bioprinted materials in research.

Before research commences researchers should anticpate the impacts of their research. Attention should be paid to research design, including assessment of the purpose and use of the research, so as to reduce risk, ethical concerns and unnecessary impacts on public health.

**Questions to ask about research involving humans:**

* Does the research involve collecting and using human cells or tissues? If so, consider the range of issues associated with collecting, storing and using human specimens and tissues.
* Does the research involve humans as participants in research? If so consider whether such participation is restricted to assessing the effectiveness and reliability of 3D printed diagnostics or also includes implanting human 3D biopprinted human cells into people for therapeutic purposes.
* Does the research involve xenografts or implants derived from other species into humans? If so, refer to any specific regulation on xeno transplantaion and use of animals in research.

**3. Sources of Cells and Materials**

A key concern in the pre-printing stage is the selection of cells to be used in the printing process. When selecting cells, lab researchers are predominantly concerned with issues around proliferation and cell culture techniques, printability, degradation, structural and mechanical properties and material biomimicry, as well as reliable cell sourcing (1). In addition to these technical and practical concerns, the inclusion of live cells introduces ethical issues related to the source of these cells which trigger different regulatory instruments.These are categorized below according to the source of the most commonly used live cells in 3D bioprinting – human, non-human animal and other (viruses/bacteria, plant) – as well as of biomaterials used in inks and as scaffolds. In addition, the section discuss issues related to donation and consent when using live cells derived from humans.

**3. a Human Sources of Cells**

3D bioprinting may raise ethical concerns resulting from the use of human stem cells. ‘The most commonly used stem cells in bioprinting are: embryonic, induced pluripotent and adult stem cells’ (13, page 1941). Human embryonic stem cells (hESC) are derived from the early human embryo, their use is controversial, with debate centering on the moral status of human embryos, as well as the interpretation of humanity and human dignity (14, 15) Concerns have also been raised about the consent or exploitation of women who donate embryos for hESC research. Many jurisdictions (for example, Australia and Canada) restrict researchers to using human embryos donated by couples or women for whom the embryos are “supernumary”, that is, the embyros were created through assisted reproductive technologies (ART) and are no longer required for the couple to achieve a pregnancy. In other jurisdictions, for example US and India (16) women may choose to donate, or sell, gametes regardless of whether they have been created for reproductive purposes. Human embryo research and the use of embryos to derive hESCs is highly regulated in many countries. In Australia, the *Research Involving Human Embryos Act* 2002 (Cth) (17) regulates use of excess human embryos created through ART.[[2]](#footnote-2) In the European Union, hESC use is subject to the Advanced Therapy Medicinal Products (ATMP) Regulation (18). Some patients consider it unethical to use 3D bioprinted materials derived from hESCs and opposition evoked by hESCs is one of the disadvantages of using these types of cells (14, page 368). In addition, innovations which fail the ‘morality test’ may be excluded from patents (see **section 6** of this chapter).

Induced pluripotent stem cells (iPSCs), sourced from adults, are not as controversial nor are they subject to the same level of regulation as those created through hESCs, and increasingly they, or alternatives to hESCs, are used in 3D bioprinting (14). The use of iPSCs does raise issues around safety and quality assurance, given the risk of cell lines derived from adult cells leading to cancers, as well as ethical concerns relating to donation and procurement. Where research uses printed cells with the aim of implanting these in a patient as a therapy, there are concerns about risks to human health and safety related to cell stability and biocompatibility. The development of 3D bioprinted therapies, requires that consideration is given to more long term effects. Health and safety questions relate to how printed cells will behave when implanted and whether they could migrate elsewhere in the body or whether cells may mutate into cancer cells (19). While use of autologous cell lines may avoid regulatory constraints associated with use of allogenic or xenogenic cells, there may still be significant risks to patients. Use of the process of producing autologous induced pluripotent stem cells (aIPSCs) has been associated with risks of teratoma formation (19). The use of allogeneic cells from donors, including from dead people, introduces risks related to potential immunological problems and the risk of disease transmission (14). .

In addition to consideration of ethical issues related to the source of human cells, researchers who use donated human tissues in research should ensure that the cell lines they use have been obtained through an appropriate process which protects the interests of the donor and that the necessary processes for securing informed consent, privacy and relinquishments of ownership rights of the donated cell or tissue has occurred (14, page 368; 20, page 14; 21). Where cell lines are derived from human embryos, there will be protocols and regulation surrounding the donation of embryos for use in research, frequently governed by legislation on ARTs. If using adult stem cells there will be different requirements for securing consent to obtain the cells and their use in research. In cases where the cells are extracted from tissue removed as part of a medical procedure, there may be no formal requirement to obtain consent from the person from whom the cells were derived. Some regulations do stress the need to obtain informed consent from a cell donor. In the Guidelines set outby CIOMS, Guideline 9 provides guidance on Individuals Capable of Giving Informed Consent (10). In the EU, specific regulation related to donation of human tissues can be found in the Tissues and Cells Directive, Article 13 (22); in the UK, the Human Tissue ACT 2004, Part 1, (23); and in Australia, in the Australian *National Statement on Ethical Conduct in Human Research* 2007, chapter 3.4 (7). An appropriate informed consent process minimizes the risk of harm and potential violation of interests, such as privacy, control of medical information and (14: 368). Further, as donated cells may survive the donors or be potentially used for projects unplanned at the time of tissue/cell procurement, donors should be informed as fully as possible about the future uses of their material and approval for use of research using this material should extend past the lifetime of the donor and/or research project (19).

In the case of donation of stem cells for research there may be problems involved in meeting the ideals of informed consent given that it may not be possible at the time of donation to foresee all future possible uses of cells lines and more general or “blanket” consent may fail to meet the standards expected of consent in research (14). When a donor is recruited for therapeutic research, comprehensive information about the 3D bioprinted product and implantation process should be provided as part of the consent process, as well as details of any conflicts of interest and potential outcomes and adverse effects (24, page 288). The privacy of the donor should be protected through anonymization of samples in scientific research (14, page 368). Questions remain about whether donors should be paid or whether donation should be free or unpaid (for altruistic purposes), so as to facilitate scrientific research ad improve public health. Some propose that altruistic donation should be the ideal behind legislation regulating the collection of cells/tissues for research in regenerative medicine (14). Questions also remain about ownership of donated cells/tissue and whether the body can be subject to property rights. Whilst acknowledging ownership rights might undergird legal processes of paid donation, and the patenting of cells and cells lines, granting ownership or property rights in tissues and organs is often considered to violate human dignity and could lead to exploitation of poor people (14, page 369; 25).

**3. b Animal sources of cells**

3D bioprinting can be undertaken with cell lines derived from animals to establish techniques for printing processes, viability of cells printed with different processes and the interaction of different printed scaffold materials with cells. They may also be integrated into 3D bioprinted therapies. The regulatory environment for deriving of embryonic and adult stem cell lines from non-humans is much less restrictive than in the case of human-derived cell lines, nonetheless, there may be animal welfare and biohazard controls to take into consideration (see **section 4** and **section 5.a** below) .

Where cells derived from non-human animals are to be used for potential human therapies (xenogeneic cells), researchers should attend to ethical concerns about the acceptability of using animal cells for research, as well as laws or regulation aimed at reducing the risk of transmission of disease across species or that prohibit the potential creation of chimeric (human – animal) organisms (26, 27). Some patients may object to receiving therapies that involve the use of cells derived from animals on religious grounds (for example, reservations of some Muslims and Jews regarding the use of porcine cells/tissue) or because of the appropriation of animals for human research and consumption (14, page 368; 18, page 14). The use of bioinks derived from xenogeneic cells raises risks including the risk of transfer of an infectious disease from animals to humans (zoonosis) and the potential immunological problems xenogeneic cells may cause (14, page 368; 18, page 14) (see **section 4**). Laws prohibiting the creation of chimeras may also apply to the introduction of human stem cells into non-human animals (28), although a number of countries permit the introduction of human cells into an animal embryo provided that the embryo is not then transferred into a human or animal for gestation (29).

**3. c Other sources of cells**

If using cells derived from viruses or bacteria, health and safety are the primary ethical concerns and researchers should attend to national and international biosafety hazard regulations, as well as bioterrorism regulations.

**3. d Bioink components**

Bioinks, in addition to live cells, involve the use of biomaterials, typically including additives (growth factors, chemicals, microfactors, others) and a supportive scaffold (hydrogels, synthetic or natural polymers).The inclusion of these materials, like of live cells, raises ethical issues related to sourcing, environmental impact andbiocompatibility. Scaffolds are not used in all 3D bioprinting approaches, however (30, page 189). Hydrogels are polymers and can be made from a variety of components, including of natural and synthetic components, including natural/synethtic combinations. Whilst the advantages of using synthetic polymers include that they can be tailored, unlike natural polymers, their interactions and effects on cells have not been studied systematically (31). Other concerns include poor biocompatibility, toxic degradation and loss of mechanical properties (1). Components of natural polymers existing in Extra Cellular Matrix (ECM) – gelatin, collagen, laminin and fibronectin, and other natural polymers such as alginate, chitosan and silk fibrin and hyaluronic acid, often isolated from animal or human tissues are advantageous given their similarity to human ECM and inherent bioactivity (31). Biomaterials derived from non-human organisms, such as gelatin (from porcine skin) or alginate (from seaweed) may carry risks, such as immunological responses and the risk of introducing pathogens (14). For these reasons, researchers need to consider carefully the materials used in 3D bioprinting, paying particular attention to risks to humans or the environment from pathogens, and risks to any human participants in the research. In deciding which bioinks and scaffolds to use, there should be consideration given to the disposal of the materials in the printing process and in their eventual degradation and impacts on the environment.

**Questions to ask about the source of cells and biomaterials:**

* Does the research involve using cells and materals from human beings? If so, consider the range of issues associated with humans as a source of stem cells – are they Embryonic, induced pluripotent or adult stem cells? In addition, consider the range of issues associated with the donation and collection of human cells, including informed consent, privacy and relinquishments of ownership. Have you familairised yourself with the regulations pertaining to donation and consent in your jurisdiction?
* Does the research involve using cells and materals from non-human animals? If so, consider the range of applicable law, regulation and ethical issues, including potential risks related to zoonosis.
* Does the research involve using cells and materials from sources other than human and non- human animals? If so, consider health, safety, and environmental impacts .
* What is the source of the materials in the scaffold - synthetic, natural or both? Do you intend to use the material in therapies? If so, consider issues related to biocompatibility, stability and degradation.

**4. Quality and Safety of Cells and Materials**

In addition to consideration of the source of cells and materials selected for use in the bioprinting process, including consent for use of human cells, consideration must be paid to the collection, storage and use of cells and materials to ensure their quality and safety. In order to ensure the quality and safety of cell and tissue material and prevent the introduction, transmission and spread of communicable diseases, the early stage of donation, procurement and testing of cells is governed by regulations. These establish donor eligibility, current good tissue practice and other procedures, including erquirements for clean processing environments. Regulations concerning the legitimate origin of cell lines for use in research will vary by country and some regulations prevent certain cell lines being used in research. In addition to these measures, to ensure the quality and safety of cells and materials, attention should be paid, throughout the printing process, to Good Laboratory and Manufacturing Processes.

Most countries’ biomedical research councils have adopted the Council of International Organisations of Medical Sciences (CIOMS) guidelines (10). Guideline 11 governs the Collection, Storage and Use of Biological Materials and related data (10). In the European Union, the EU Tissues and Cells Directive, sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (22). In the United Kingdom, the Human Tissue Act 2004 regulates the removal, storage and use and disposal of human tissue, overseen by the Human Tissue Authority (HTA) (23). In the US, therapies derived from human cells and tissues intended for transplantation in use in a human are regulated as human cells, tissues and cellular and tissue-based products (HCT/Ps). The Code of Federal Regulations (CFR) Parts 1270 and 1271 require tissue establishments to screen and test donors, to prepare and follow written procedures for the prevention of the spread of communicable disease, and to maintain records (32).[[3]](#footnote-3) In Australia the use of human and animal cell lines in health and medical research is covered by guidelines and statements issued by the National Health and Medical Research Council (7). Researchers should abide by the provisions in the *National Statement on Ethical Conduct in Human Research* 2007, chapter 3.4 Human biospecimens in laboratory based research. In Australia, regulation of therapeutic goods is governed by the Therapeutic Goods Administration (TGA) in accordance with the Therapeutic Goods Act 1989. Therapies derived from 3D bioprinted materials would fall within the category of “biologicals”, and researchers should be aware that this is an area of regulation that is regularly undergoing changes in light of the emerging science. (see **section 6** below).

Sterilisation of the environment, materials and machinery is important for ensuring cell safety and quality. The use of an asceptic environment extends to cell culture and biofabrication machinery (8, pages 23-24).3D bioprinting must be performed within a regulatory framework of Good Laboratory Practice (GLP) for standardized, optimized and controlled tissue fabrication. GLPs vary by Country, see the World Health Orgnanisation (33), the United States (34) and the European Union (35). If you are printing material for use in humans, then adherence to the more rigorous Good Manufacturing Practice (GMP) for clinical-product development is required (cf Preface, Crook). When using 3D bioprinting techniques for biological applications, sterilisation of the environment, materials and machinery is of absolute importance to prevent contamination of 3D bioprinted products. GMPs regulations vary by country and are overseen by regulatory agencies – see World Health Organisation (36); the United States (37) and European Union (38).

**Questions to ask about ensuring the quality and safety of cells:**

* Are you aware of the range of issues related to the safety and quality of cells, including regulations around procurement, storage, disposal and record-keeping?
* Are you familiar with Good Laboratory Practice and conduct around ensuring clean processing environments?
* Are the tissue products intended for use in humans? Then have you consulted the specific regulations? Are you familiar with regulations related to Good Manufacturing Practice?

**5. Testing the Safety and efficacy of 3D bioprinted materials:**

Once the biomaterials have been printed, issues will arise with respect to testing the safety and efficacy of these materials. This may involve the use of animal and/or human trials. It is possible that future development of 3D bioprinting techniques, for example, using autologous human cells to print organ tissues, will avoid ethical concerns associated with organ transplant rejection and potentially reduce organ waiting lists and the illegal trade in human organs, or provide alternatives to drug and vaccine testing on animals and humans. Similarly, *ex vivo* testing on 3D bioprinted animal or human tissues amy reduce the dependence on use of humans and animals in *in vivo* tests. In the meantime however, trials using animals and humans will remain the standard models for testing the safety and efficacy of novel materials and devices.

**5. a Animal Testing**

Having secured a cell line and printed live cells into a 3D structure, researchers may seek to conduct tests to establish the reliability of diagnostics, the biocompatibility of the materials or the efficacy of a therapeutic. Any animal study will be governed by regulations as discussed below. Where researchers are developing 3D bioprinted materials for implants, researchers need to consider whether all the materials are safe to implant in the human body. They will need to assess the stability, biodegradability and biocompatibility of the materials, and test the behavior of cells and scaffold materials, including assessing cell migration and mutation, the potential for immunological reactions, the long term health effects, including the potential for teratoma and cancer, the dislodgement and migration of implants, as well as cell and material stability or degradation. These questions are usually determined using a pathway starting with *in vitro* trials to establish whether the new 3D bioprinted materials (and devices) are safe for use. These will then be followed by clinical trials on animals to establish both biocompatibility and effectiveness before being tested on humans.

The use of animals in research requires ethical justification, see, for example, the Australian Code for the Care and Use of Animals for Research (39). While 3D bioprinted tissues for diagnostic testing may result in a reduction of the total number of animals used in research, thorough testing of diagnostic and therapeutic uses of 3D bioprinting will still require trials on animal before testing in humans. Since the latter half of the 20th Century, there has been increasing concern about the use of animals in medical experiments and research (40). The recognition that animals experience discomfort and pain demands that the use of animals should be minimized and any unnecessary suffering should be avoided. Regulatory frameworks for the use of animals adopt the principles of replacing, reducing and refining the use of animals in scientific research (39).

In most countries, laws, regulation and guidelines addressing the care and use of laboratory animals require researchers to obtain approval of their research from animal research ethics and welfare committees to assess whether the use of animals in the proposed research is justified and appropriate. The UK has some of the strictest protections, writing its ethical framework into law by implementing The Animals (Scientific Procedures) Act 1986 (41), which requires experiments to be regulated by three licences - a project licence for the scientist in charge of the project; a certificate for the institution and a personal licence for each scientist or technician. In addition, all licensed establishments must have an Animal Welfare and Ethical Review Body (AWERB). In Australia,Animal Ethics Committees (AECs) oversee and have authority to approve the use of animals in research within research institutions. AECs follow the Australian Code for the care and use of animals for scientific purposes (39). In the US**,** animal testing on vertebrates is primarily regulated by the Animal Welfare Act of 1966 (AWA) (42) and the Animal Welfare Regulations (43). In addition, the AWA requires institutions to maintain an Institutional Animal Care and Use Committee (IACUC) to ensure local compliance with the Act. In the EU**,** experiments on vertebrate animals (since 2013) are subject to Directive 210/63/EU on the protection of animals used for scientific purposes (44). In Japan the main law is the “Act on Humane Treatment and Management of Animals,” which mandates a self-regulation system for animal experimentation (45, page 303). In addition, there are numerous voluntary guidelines provided by various organizations. Animal research in China is currently regulated and administratively managed according to national and provincial laws, regulations, guidelines, and standards (45, page 303).

**Questions to ask concerning animal testing:**

* Does your research involve testing on animals? If so, have you considered the range of issues related to reduction, replacement and refinement of the use of animals in research?
* Do you need to obtain ethics approval from an Animal Research Ethics Committee?
* Have you obtained the necessary licences?

**5. b Human trials**

Once preliminary biocompatibility and safety tests on animals indicate that the 3D bioprinted materials are not harmful and have been shown to be effective in principle, the safety and effectiveness of new diagnostics and therapeutics is then tested on humans in clinical trials. Approval to undertake clinical trials requires independent ethical review, in the US, Institutional Review Boards (IRBs), in Canada, Research Ethics Boards (REBs) and in Australia, Human research Ethics Committees (HRECs). Approval of a drug, device or diagnostic tool for sale or use in clinical settings requires the additional registration and approval through national drug and therapeutic good regulators such as the US Food and Drug Administration (FDA) or the Australian Therapeutic Goods Administration (TGA) and through regulations such as the EU Medical Device Regulations (46).[[4]](#footnote-4) In the development of 3D bioprinted diagnostic devices, for example, a clinical trial of the device would seek to establish that it met an appropriate threshold of reliability initially, with later trials establishing, for example, that it was as well or better accepted by patients (in terms of discomfort or inconvenience), that it was no more costly and allowed for earlier or more fine-grained diagnosis of the relevant condition. The research ethics review process would be governed by principles designed to protect the interests of participants in research, while the overarching drugs and therapeutic goods regulation is designed to protect the wider group of people who may rely on the diagnostic device in clinical contexts. Reference should be made to human research regulations cited in **section 2**. Some jurisdictions have separate regulations which pertain specifically to clinical trials. These should be considered alongside human research ethics guidelines.

Clinical trials are subject to various regulatory controls to ensure the safety of participants, however, the personalized nature of 3D bioprinted products may challenge the use of randomized clinical trials as the primary means for testing new medical products and devices. At present in Australia, for example, there is no specific regulatory framework to guide the testing of 3D bioprinted treatments in human patients. Traditionally, the safety and efficacy of an experimental treatment has been established through progressively larger samples of patients receiving either the experimental treatment or a placebo to establish a statistically significant effect of the experimental treatment, More frequently now the experimental treatment is compared with the most effective treatment currently available. However, where the experimental treatment involves a number of new variables such as a new surgical technique to implant 3D printed devices as well as the possibility of using the patient’s own cells as the source of the printed cells, it may be difficult to adapt the clinical trial methodology to provide meaningful evidence of safety and efficacy unless the complex array of novel interventions is broken down into more specific trials. To the degree that the novel treatment is individual to the patient, for example using her cells and designed around the particularities of her organs or physical structure and involves assessing a very complex array of novel factors, including surgical methods, and the interaction of new materials with her biochemistry, as well as, conceivably, new drugs that are delivered in new ways, then the trials of the various elements may not be able to be assessed discretely (8, page 50). New methods for evaluating 3D bioprinted therapeutics for clinical approval will be needed which assess the complex array of technique, materials and functions, and which acknowledge the limits of generalisations based on clinical outcomes given the differences between individual patients (8, page 50).

**Questions to ask concerning human testing:**

* Does your research involve testing on humans? If so, do you need to obtain ethics approval from an Independent Review Board Human Research Ethics Committee?
* How have you designed your trial to ensure the quality and significance of the findings while also protecting the interests of research participants?

**6. Classification and patenting of 3D bioprinted products**

**6. a Classification of 3D bioprinted products and devices**

Where the focus of research is on the final translation of 3D bioprinted research into clinical practice, a key issue in post-printing will be the classification of bioprinted products in order to assess the appropriate regulatory mechanism for approval of the product. Regulatory regimes have tended to define therapeutic products as single entities with respect to their use and functional aspects – for example, as a pharmaceutical, biologics or medical device (47, page 2). 3D Bioprinted products and approaches, by combining components or sharing features from one or more of these categories, challenge the demarcations between regulated product categories. For example, a 3D bioprinted product may combine cell laden tissue products with a device, potentially also with a drug delivery mechanism. Under some regulations, 3D bioprinted products are often described as combination products – broadly defined as containing one or more regulated components (47, page 1).

In Australia, the Therapeutic Goods Administration (TGA) is responsible for regulating therapeutic goods under the therapeutic goods legislation. This legislation refers to classes of Medical Devices and Biologicals, the former classified in the Therapeutic Goods (Medical Devices) Regulations 2002 (48) and the latter, Therapeutic Goods Regulations 1990*.* The TGA treats therapeutic products developed from 3D bioprinting as a ‘borderline’ or ‘combination’ treatments which is part medical device, part biological (50). The Australian Regulatory Guidelines for Medical Devices (50) and Australian Regulatory Guidelines for Biologicals (ARGB) are also relevant.[[5]](#footnote-5) In the EU, therapeutic products are classified as either medicinal products or medical devices; both the Advanced Therapy Medicinal Products (ATMP) regulation (18) and Medical Device Regulations (46) are relevant. The ATMP Regulation classifies tissue-based or cell-based products as medicinal products, including gene therapies, cell therapies and tissue engineering (6, page 9; 52, page x).In the US, the FDA classifies therapeutic products as pharmceuticals, biologics and medical devices, each of which is overseen by a diffent section of the FDA – the Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research; and, Center for Devices and Radiological Health, respectively. 3D bioprinted therapeutic and diagnostic products may be considered by the FDA as a “combination product”, when it includes medical devices that combine of biological materials, medical devices, and/or drugs of different compositions (53). Given the rapid progress aand novel applictaions of 3D biorpinted technologies, many relevant regulations are either currently under review or will be revised soon. Researchers should be aware of the rapidly evolving and changeable regulatory framework for calssifcation of 3D bioprinted technologies.

Software and hardware set ups for 3D bioprinting may be regarded as medical devices (that would then fall within the relevant regulations, for example, the EU Medical Device Regulations). If so, software and hardware setups will need certification before being released on the market (6, page 8). This would mean software would fall subject to safety and performance requirements and also raises data protection issues.

In addition to concerns about classification, combination products raise issues related to consumer safety and protection. A combination product will command a high level of regulatory scrutiny, particularly for the manufacturer that makes multiple constituent parts. The key regulatory focus areas for combination products are: the process from design to manufacture; software system chain control and validation; and potential variation in critical quality attributes (CGAs) of the final manufactured product (47). The mass digitization of STL (stereolithography) files pose risks to the regulatory framework of consumer safety, product liability (quality control), and data protection, confidentiality and safety (6, page 7; 47; 52).

**6. b Intellectual Property and Patenting**

Researchers should be aware of the relevant Intellectual Property (IP) framework and the requirements to protect their interests prior to publishing their research or moving to clinical trials. Relevant areas of focus include: machines, methods, materials, processes, and products (eg kidney cell). There is uncertainty within the IP legal landscape for bioprinting including uncertainty over what aspects can be protected, as well as which aspects of patentability and copyright should not be protected for ethical or public policy reasons.

The law around patenting in the 3D bioprinting area is evolving. The potential for patenting of 3D bioprinting technologies is a contentious matter and a topic of contemporary legal and ethical discussions (52, 54, 55). Patentable subject matter is that which is new (novel), useful (industrial application or utility) and contains an inventive aspect or step (54). Patents could apply to methods of 3D bioprinting and to 3D bioprinted products, including bioprinters, bioprinted materials, as well as the fabrication and postproduction maturation processes. Given the customized nature of 3D bioprinting, patents over methods or processes are likely to be predominate. In contrast, given the personalized or bespoke nature of 3D treatments, patenting of 3D bioprinted products may be less useful and so less likely (54). However, whether innovative methods and products used in biomedical inventions constitute patentable subject matter is not clear. For example, many jurisdictions exclude patenting of human beings or tissue. In some jurisdictions, patents are not extended to products that are identical to the natural element, although materials isolated from the human body or otherwise produced by a technical process may constitute a patentable product. With reference to these directives 3D bioprinted tissues using hydrogel and a scaffold may be patentable but a 3D printed organ produced by 3D scanning and CAD files may not be (52, page 288). Patents have been granted for 3D bioprinted technologies (including for processes and products, for example ‘Multilayered Vascular Tubes’ by Organovo (52, page 286).

However, given the natural elements of the product itself, many argue that IP law should not apply to 3D bioprinted products; that, these technologies should not be protected. Whilst patents may protect the inventions of researchers (and investment by companies), patents applied to 3D bioprinting technologies would prevent others from making, using or selling patented methods and products. This raises ethical issues related to access and benefit sharing of these technologies, they may restrict patient access to medical treatment and potentially hinder innovation (create barriers to innovation and access to health). As in the area of genetic technologies and diagnostic testing patent granting has had monopolistic effects which have widened gaps in health (52, page 283; 54). In the interests of access and equity to health technologies some countries have introduced exclusions from patentability, including based on a “morality test” and whether methods constitute medical treatment or therapy. The European Patent Commission, for example, excludes the commercial exploitation of an invention, if such activities are deemed to offend against the standards of morality (52, page 287; 56). Existing Patents laws in India contain an exclusion criteria according to contrary to public order or morality (57). Exemptions for methods for medical treatment or therapy may include diagnostic methods, or may not, depending on how these are defined (52, page 293) and whether the diagnostic method is *in vitro* or *in vivo* (under UK patent law, the former is patentable). In the US, patents for medical treatment have been more commonplace, although therapeutic exemptions exist and, in recent years, the approach in determining the scope of patentability has been more strictly adopted (52, pages 293-4; 54).

To develop an equitable approach to innovation and benefit sharing of access to health technologies, alternative governance models to patents have been canvassed (52, 54). These include the adoption of a portfolio approach to innovation (52). Others advocate limited patents over some over certain elements of bioprinting.

In contrast to 3D bioprinted products or processes, copyright protection might be more applicable to. developed software rather than patent protection. Copyrights would protect the CAD-CAM files used in 3D bioprinting for scanning, manufacturing and bioprinter control. Although, copyright laws maye be inadequate; trademark law for hardware and software protection and trade secret protection may present some avenues for bioprinting rights. Similar ethical issues to those of patenting – concerns related to equity and access – are raised with respect to copyrighting 3D bioprintings software. For example, if a sotware is developed that allows for printing functional organs, for the benefit of society, iuts availability should not be restricted.

Given the evolving legal landscape, as well as the specificities, researchers should liaise with the IP and patenting office at their Institution or Research Facility.

**Questions to ask concerning bioprinted products (and processes):**

* Does your research involve the development of a bioprinted produce that will require regulatory approval before it can be used clinically.
* Have you considered the regulatory requirements early in the design of your 3D bioprinted devices or therapy?
* Will your research innovate a 3D bioprinting product or process, have you considered the IP environment and requirements for asserting IP or for commercialising your research?

**10. Conclusion**

3D bioprinting presents real possibilities for understanding, diagnosing and developing new therapies. 3D printed cells and living structures are being used in medical research, in vitro drug testing and as *in vivo* transplant materials. The incorporation of live cells in the printing process raises ethical, policy and regulatory issues at all stages of the bioprinting process, relative to the purposes of research and application of the research. This chapter has focused on the ethical and regulatory issues that arise in the 3D bioprinting process seeking to assist researchers in the lab to consider the ethical and regulatory issues at each stage. This chapter identified ethical issues in relation to the use of humans and animals in research; the source of materials and cells; the quality and safety of cell and materials; donation and collection of human cells; the testing of materials, and animal andclinical trials. It also identified regulatory issues related to the classification of 3D bioprinted materials and products, and Intellectual Property and Patenting.

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1. This chapter does not discuss approaches to bioprinting, nor particular printing techniques; these are discussed in part B of the volume. [↑](#footnote-ref-1)
2. The Research Involving Human Embryos Act 2002 regulates only the derivation of human embryonic stem cells from excess ART embryos). Research involving the use of human embryonic stem cell lines, including human embryonic stem cell lines that have been imported into Australia, is not subject to specific regulation. [↑](#footnote-ref-2)
3. Bioprinted tissues typically used in research do not require FDA approval during animal and in vitro testing because they are not intended for use in humans. [↑](#footnote-ref-3)
4. New Regulations on medical devices were adopted in 2017, replacing existing Directives. The new rules will apply after a transitional period. [↑](#footnote-ref-4)
5. Note, at the time of writing ARGMD is currently under review. [↑](#footnote-ref-5)