

Ethical guidelines for using bioprinting for humans

Laetus OK Lategan^{*1}, and *André F van der Merwe*²

¹Central University of Technology, South Africa. llategan@cut.ac.za

²Stellenbosch University, South Africa. andrevdm@sun.ac.za

Abstract: This paper's focus is the identification of ethical guidelines for bioprinting for humans in addition to existing bioethical principles and guidelines. The literature review explores the definitions for additive manufacturing and bioprinting and the application extent of these technologies. From this review, ethical challenges were identified and discussed. The purpose of the paper is to guide scientific research, practitioners, and relevant healthcare workers through various ethical viewpoints, and to point out the consequence and effects when applying newly discovered technology. Due to the complexity of bioprinting, additional guidelines were identified to cover the scope of bioprinting in bioethics. Consequently, four sets of ethical guidelines for decision-making in bioprinting were identified with person-centred ethics at the core of these sets.

1. Old wine in new wineskins?

Discussions on ethics and technology are not new. Neither are the existing guidelines no longer in use. Van den Berg (1969) [1] drew our attention to the consequences of technology in medicine with his seminal comment that we should not do everything that we have the knowhow for.

However, the existing ethical guidelines may not be sufficient to cover new developments due to, amongst other, the Fourth Industrial Revolution (4IR), also known as Industry 4.0. Throughout the South African Presidential Commission Report on the Fourth Industrial Revolution (4IR) [2] it is stated that people are playing an important role in 4IR. The report is clear that ethics cannot be neglected in the discussion on and development of 4IR technologies and practices. In fact, ethics should become part of a programme on human capacity development.

When using technology in healthcare, then it is not only the *abilities* of technology but also the *impact* and *consequences* of technology on healthcare that should be considered. This impact is so dominant that according to Creplet [3] it brought a third revolution in healthcare about. Within the 4IR the benefits for health and healthcare are acknowledged but requires ethical guidance on these developments. The World Economics Report on health and healthcare in 4IR (2019) comments that:

*Corresponding author: llategan@cut.ac.za

“The rapid advances in science and technology are accelerating the need for ethical norms and standards to govern behaviour. It is important that the scientific community engage different stakeholders, including the public and social, ethical and religious groups to develop norms and standards for conduct that distinguish between acceptable and unacceptable behaviour” [4].

This observation already suggests that ethicists should keep on digging deeper to identify relevant principles and guidelines for these new developments. It is not so much the technology itself that draws the ethicist’s attention, but technology’s *application* as it impacts on humans and their environment.

An emerging technology (around 1981) often ignored in the discussion on technology and ethics is *additive manufacturing* (AM) used for humans. AM refers to the *process of building parts by adding additional material mostly in layers*. A more specific definition is that AM describes the technologies that “build 3D objects by adding layer-upon-layer of material, whether the material is plastic, metal, concrete or human tissue” [5]. AM developed exponentially since the 1980s. Initially, *inorganic* materials were used for 3D printing, recently followed by *organic* materials. Bioprinting emerged from this new development. Using organic materials in three-dimensional (3D) printing is an exciting new development, especially for tissue engineering and experimental biology. Miller remarks that regardless this excitement, for bioengineers the probing question is if the created structure from living tissue will lead to the desired function [6]. This is still a question that must be resolved.

Although there is no shortage of publications on the many aspects of AM, there is only the last decade or so a growing discussion on AM in the context of bioethics, especially where stem cells and human tissue are used. In South Africa, there is a limited discussion on this topic as observed in the online platform, Sabinet African Journals (<https://journal.co.za>). This is in particular true of bioprinting [7]. Hence, the growing need for bioethics guidelines for bioprinting used for humans [8]. Afterall, the fundamental goal of regenerative medicine is improving patient welfare [8]. Ethical guidelines should therefore be clear. Paragraph 3 will return to bioethical challenges associated with AM and bioprinting.

Against this background, is this paper’s focus on bioethics guidelines when bioprinting is used for humans. This paper wants to identify bioethics guidelines, especially for the South African context, and create a platform for further discussion in South Africa on this topic. The position is taken that the ethical guidelines emerge from two ethical markers, namely *customisation or personalisation* and *access to healthcare*. The first marker is relevant for a person-centred ethics and the second marker on equity and fairness in healthcare.

In this paper, bioprinting will be unpacked, analysed, and interpreted in the context of bioethics focusing on human beings.

2. Conceptualisation and benefit

In general, AM creates objects by “adding” material following the 3D model dataset. Terminology standard ISO/ASTM 52900 defines AM as “the process of joining materials to make parts from 3D model data, usually layer by layer” [9]. From the annual Wohlers Report is AM known by names such as 3D printing, additive fabrication, direct digital manufacturing, freeform fabrication, solid freeform fabrication, rapid manufacturing, and rapid prototyping [10]. Fanucci, Barwick and Prinsloo [7] refer to 3D printing as “an interdisciplinary technology” that holds benefit for medicine.

A fast-growing development in 3D printing is *3D bioprinting* or *biomanufacturing*. Vijayavenkataraman [11] defines bioprinting as a 3D printing technology with material that incorporate viable living cells. A recent example was the first known transplant of an ear printed from human cells [12] using 3D AuriNovoTM implants [13]. Gilbert, O’Connell and Mladenovska [14] refer to bioprinting as a “dual use technology” as it presents both *benefit* and *risk*. Bioprinting is *individualised* and presents benefits for *personalised* treatment. Although this is an advantage, it is also a shortcoming as the same printed product cannot be used by other people to. Bioprinting is therefore personal, unique and cannot be repeated. Fanucci *et al.*, [7] explain bioprinting as the fabrication of tissue constructs making use of 3D printing.

Vermeulen, Haddow, Seymour, Faulkner-Jones, and Sue [15] are helpful to conceptualise bioprinting. They comment that although bioprinting and bio-fabrication are often used interchangeably, they are not the same although there is an overlap. Bio-fabrication is different from bio-mineralisation and is further distinguished between bioprinting and bio-assembly. Bio-assembly is used for tissue engineering and regenerative medicine. They use the Oxford Dictionary’s definition for bioprinting namely materials incorporating viable living cells [15]. Short term advantages include gains from tissue engineering such as artificial skin, printing of bones, part of the ear and heart valves and excluding animals in testing. Long term gains are also excluding animals in testing and avoiding the possibility of the so-called “yuck” factor that is an intuitive negative appreciation of something that can be potentially harmful. In return they encourage a more robust debate instead. Other long-term benefits are the reduction of cost of organ transplantation and the ethical double sword – someone has to die for someone to live. Another benefit is bioprinted transplantations for the youth [15]. Bioprinting is not without its benefits. Vermeulen, *et al.*, [15] comment that bioprinting is a ‘game-changer’ as living or deceased donation or animal transplantation is no longer needed. They are also mindful that bioprinting cannot go without ethical guidelines. Consequently, they present a possible ethical framework, called “Responsible Research Innovation” as an oversight model for 3D bioprinting. The focus of their oversight model is based on aligning research and innovation with society’s values and expectations and the joint responsibility between researchers and society for the development and outcomes of the research and innovation.

The wider definition of bioprinting would include the layer-by-layer addition of organic material to create a predefined shape. It would exclude the creation of a shape using inorganic materials. It would also exclude the creation of a shape which is formed by the material re-organising itself with or without external intervention.

From these comments can be concluded that both the application of the technology and possible consequences of using this technology for humans spark bioethical challenges. The pointer is that not only the technology but also the material (or “bio-ink”) should be evaluated for ethical issues. Bio-ink refers to as combining cells and extracellular matrix as “ink” [6].

The next paragraph will identify the bioethical challenges associated with bioprinting.

3. Bioethical challenges associated with bioprinting for humans

Ogoh performed a literature review on ethics and AM and reports ten prominent themes raising ethical challenges. These themes are environmental issues, health-related issues,

safety issues, intellectual property rights, 3D printed weapons, employment issues, bioethical issues, information security, liability, and biohacking. He continues to comment that not all interviewees in his research on the topic are of the opinion that there are no ethical concerns associated with AM. However, commentaries on specific matters raised the reality of ethical concerns [16].

In general, ethical challenges arise with using human tissue or in the manufacturing process using 3D printing. This is true, when, for example, donor human tissue is used without knowing any underlying conditions of the donor. In addition, application challenges are associated with the violation of human rights, vulnerability caused by the application, and access to medical care.

Bioprinting is personalised medicine. Where bioprinting is replacing damaged organs, it is considered as less of an ethical matter, but the tissue used, for example, that of animals, raise ethical matters [16]. A more responsible AM can address these concerns [16]. Enabling factors such as education, enviro-friendliness, IP rights and transparency in business can promote ethics in AM [16]. He makes an important observation: The ethical unique nature of 3D printing is a result of the hacking culture and the context in which the technology is used [16].

Hooper [17] states that 3D printing has made strides in medicine to make technology more human-friendly as evidenced by, for example, prosthetics developments that are customised and cheaper. Her worry is, however, that ethical concerns associated with ongoing developments in 3D printing may be ignored. One example is possible security risks associated with hacking into the 3D file and adjusting specifications which may not be known until after the implant. The high cost associated with 3D technology developments in healthcare is another concern. The rightful question is asked if this is a technology for the rich only? Safety is another concern. The potential risk of implants manufactured with titanium is already known. Organ transplants are more challenging to declare them as safe treatments. What about manufacturing organs but bank them for another day? There is no doubt that there should be regulation as some technologies are essential whilst other such as cosmetic surgery may be more optional. Hooper acknowledges that some comments may be futuristic but emphasises that ethical guidelines should be developed alongside with 3D technologies due to the speed of their development. Simana [18] adds to these discussions raising the issue whether 3D bio-printed organs should be treated as property. Specific medical ethical questions relate to if life expectancy should be extended, for example: Which bioprinting applications should be regarded as treatment or enhancement? Will an entire population have access to these organs? Does 3D printing change the definition for being “human”?

Gilbert *et al.*, [14] identify five specific ethical questions relevant to organ bioprinting. These questions are (a) What are the limits for bioprinting? (b) What are significant harms? (c) Is the clinical trial paradigm safe? (d) What is the ethics of irreversibility, loss of treatment opportunity and replicability? and (e) What specific framework is needed for the regulation and testing of 3D bioprinting treatment? Two important comments are whether any biological “items” should be printed and if any biological “ink” should be used. Another consideration is to interpret “harm”. For example, what is the potential of harm to emerge, what will be the gravity of the harm, who will suffer from the harm? Ethical issues can also be raised when for example embryo tissues or animal tissue is used as bio-ink. The importance of this discussion is that the more the laboratory experiments will translate to clinical use, the better equipped bioprinting practitioners will be to identify ethical risk.

Dodds [19] lists three challenges with using stem cells, namely (a) justice in access to healthcare, (b) potential harm and (c) if the capacity of individuals may be enhanced beyond what is “normal” for humans. Personalised medicine’s advantage is that it directs a specific need for which general treatment is not readily available. The challenge with potential harm or risk is on knowing whether the treatment will be safe because stem cell therapy cannot be tested on more people as a person’s own cells are used. Models for testing for safety and effectiveness should be identified. She raises another ethical concern. For the military, for example, it will be quite useful to use 3D printing technologies to protect soldiers from injury. This in return may lead to the development of another kind of weapon that can be more destructive. As a result, increase the vulnerabilities of civilians.

Kirillova, Bushev, Abubakirov and Sukikh [20] refer to 3D bioprinting of tissue-engineered constructs and prototype organs for regenerative medicine as “one of the most rapidly developing and promising areas of biotechnology”. As example they use “artificial ovary biofabrication.” This example involves the well-being of the patient and future children. This example refers to human enhancement through technological improvement. It can be interpreted as “radical transhumanism” and is exemplary of utilitarian ethics focusing on the “individual’s desire for self-improvement and a better life”. Looking at the practice of allogeneic cell transplantation, the known ethical donor problems are (a) the confidentiality of the donor, (b) the donor’s informed consent, (c) the cell production procedure, and (d) donor cell ownership. In judging the ethics of this challenge, then the moral nature of the action will be considered together with the agent’s intention, the cost of the action, what effects there might be and the balance between good and bad effects. It should also be remembered that the commercial use of embryo cells is a taboo. Human rights protection in the field of biomedical research is based on two principles, namely *informed consent* and *confidentiality*. Using bioprinting can challenge health (for example, organs) or quality of life (for example, reproductive organs). Eventual commercialisation of bioprinted organs can also trigger ethical challenges. The bottom line is the safety, quality, and efficiency of bioprinting technologies respecting human rights and dignity. Moreover, it is necessary to develop requirements for safety, quality, and efficiency of technological procedures and the end products obtained by 3D bioprinting considering human rights and dignity.

Vermeulen *et al.*, argue that ethical challenges are related to the cost of treatment, over expectation of the availability of solid organs such as kidneys and liver, and the absence of *in vivo* studies identifying potential risks. The ownership of bioprinted organs should be added to these challenges. They promote an upstream engagement between ethics and society. Their advocacy is the alignment of research and innovation to the values, needs and expectations of society. This means that scientists and the public are reacting appropriately to each other. They also take joint responsibility for processes and outcomes of research and innovation [15].

From these comments, the observation is that bioprinting are a useful addition to AM technologies, but its application should be subjected to acknowledged bioethical guidelines to avoid risk and harm.

4. Ethics in technology

Ethics is commonly understood as the difference between “good” and “bad”. Scientifically, ethics is the *study of moral principles* leading to our decision on what is “good” and “bad.” Ethics is therefore generally understood as the principles which are universal accepted to

inform and contribute to the well-being of society.

Within 4IR, artificial intelligence is a dominant concept. A burning discussion within 4IR is whether “machines” can behave responsibly? To what extent can machines operate based on morality, values, and care? In his book, “*Machines behaving badly: The morality of AI*” Toby Walsh [21] raises questions about the unintended consequences of Artificial Intelligence (AI).

Discussions on ethics in technology, start with two observations: *Who* is building machines? and *What* can these machines do? The “*who*” raises the question if machines are portraying “characteristics” of their “builders”? The “*what*” raises the abilities of these technologies. Are these abilities ever considered?

Ogoh [16] identifies four criteria to assess the ethical challenges in AM. These are business concerns, environmental concerns, resource concerns and information concerns.

With this as background, when applied to bioprinting, one should be mindful of the four guiding principles for bioethics identified by Beauchamp and Childress [22], namely: *autonomy*, *beneficence*, *non-maleficence*, and *justice*. Although these principles are generally regarded in healthcare as the backbone for ethics in health- and medical-related activities, the content is relevant for all ethics discussions.

From the discussions in this paper, the question is if the four principles above are sufficient for bioprinting or are more required? Or is it rather a case of clarifying the application of these principles to bioprinting? The next section will consider these questions.

5. Ethical guidelines for bioprinting

In general, this paper recommends the bioethics principles identified by Beauchamp and Childress for bioprinting [22]. However, the complexity of the technology and the human tissue and cells that can be used, require an elaboration of these principles.

From the discussions in this paper, the following ethical guidelines for bioprinting can be identified:

- “Doing the right thing” is based on both *personal morality* and *ethics*. Personal morality is grounded in religion or a belief system, world and life orientation, culture, association with a group and orientations towards responsibility, duty, and obligations. In essence, what is the individual’s *own* view regarding what is right and wrong. Ethics on the other hand, is value-based systems and orientations that are applied to make the right decision. Ethics has a broad orientation towards scientific disciplines, professional behaviour, schools of thought, and universal values influencing ethical orientations. The broad schools of thought are *virtue ethics* (defining principles), *deontology* (action and behaviour), *utilitarianism* (greatest amount of good for the greatest number of people) and *consequentialism* (application of principles). Universal values embody principles such as dignity, social justice, the right to life, access to medical care, clean water and food, personal security, and protection to name a few. An important feature of universally accepted norms is that they transcend religion, cultures, regions, and group identities and constitute common morality [23]. The four bioethics principles identified by Beauchamp and Childress are representative of a universally accepted value system

(see paragraph 4). A *first* guideline is that the distinction between morals and ethics is important to secure fairness in decision-making. In general, are universal values broad enough to respect individual morals.

- Next to morals and ethics, *integrity*, and *professional standards*, should be added. Integrity refers to the way in which an action is performed. It calls for fairness, honesty, and decency. Integrity also relies on the public's trust in how a particular decision is arrived at. Consequently, is the transparency of discussion and decision-making important. Integrity is personalised and should not unlawfully be influenced by external factors such as politics or the economy. Professional standards are important as these standards are the minimum values a profession should adhere to. Varkey [23] links professional conduct and codes to research ethics, public health ethics, organisational ethics, and clinical ethics. Different types of ethics are relevant for bioprinting as bioprinting depends on a range of activities such as design, product development, manufacturing, and implantation. The above professional standards should be extended to include ASTM and ISO standards, standard operating procedures, and process validation. The reason being that these standards can help to mitigate ethical and legal issues in bioprinting, as identified by Kirillova *et al.*, [20].

It is further recommended that a well-functioning quality management system, including policies and procedures, standard operating procedures, and process, product and software validation are key to promote the market uptake of bioprinting. A *second* guideline is to link integrity, professional conduct and professional standards and procedures to the manufacturing of bioprinted parts and the decision to use these parts. To this decision should a full product and process risk management assessment be linked to identify what the residual and remaining risk levels are. This will inform the decision how to use these parts.

- Humanity is interwoven with ethics. In the context of bioethics, are values such as respect for own life choices on condition that it is safe, has minimum consequences, avoids self-harm, advances life, and promotes dignity and respect for own life and that of other people closely associated with humanity. Although the baseline for all ethics is to do or cause no harm, advancement should be added as another baseline. Most people in need of medical interventions are because the quality of their life is challenged. In return should ethics challenge those determinants contributing to a compromised quality of life. A *third* guideline is that the quality of life should never be harmed or put at risk.
- The discussion on how medical resources should be allocated, is well-known. Whilst it is commonly accepted that prevention of disease is high on the healthcare agenda, healthcare cannot be reduced to basic healthcare either. The advancement of healthcare is based on, amongst others, the improvement of medicine and medical therapies. Again, a balance is required between what is a desire and a need, what is aimed for and what is the reality. What should be reckoned with is the long-term prognosis and the potential survival rate. The guiding principle is that money cannot buy health, but it can improve health. A *fourth* guideline is that there should be a balance between basic healthcare and the advancement of technology to add to the quality of life.
- A combination of *deontology* (respectful duties) and *utilitarianism* (greatest good) can inform the discussion on the development and application of technology in particular AM and bioprinting. Ethics should always consider what is good for an individual as well as the group. Respectful humanity can never save or improve only the life of a few

people but should always have the interest of as many people as possible at heart (*utilitarianism*). Bioprinting can never be developed to benefit those people who can afford it only. At present, bioprinting is an extremely expensive technology. Its development can never be at the expense of other medical interventions that can benefit many more people. A *fifth* guideline is to balance the relationship between the interests of the individual, an interest group, and a population.

- Healthcare is about the common good. What bioprinting can *do* (in theory) and what is *required*, should also be balanced. From a public health perspective where the focus is on prevention rather than cure, bioprinting may not be in demand. In a society where the public health system already has challenges to deliver on access to quality healthcare, bioprinting cannot be a priority given the baseline requirements to sustain healthcare. However, new therapies are important to improve already existing interventions. The “cost” associated with development can never be regarded as unnecessary when the long-term aim is improving the health of a population suffering from a particular disorder.

Taylor [24], from a business context, refers to “tweaking the value propositions.” This is where cost is considered against benefit or when something is done for people instead of taking things away from them. Taylor’s advice is to distinguish between economic and human values, what can be done, and what should be done. From his view, the guiding principle is that promoting something new is often a case of adding value instead of reducing it. It can be stated that it is unethical to spend a budget on a technology that will benefit only a few. However, advancement cannot be considered for some direct beneficiaries only. A publication by Zimmerling and Chen [25] serves as an example. They describe in their article how bioprinting may contribute to combating infectious diseases by focusing on *in vitro* modelling and the development of therapeutic agents and vaccines. Bioprinting can create constructs that can serve as *in vitro* tissue or virus-disease models in combating infectious diseases.

Another consideration in this discussion is although cost versus benefit is an important consideration, an equally important consideration is if the benefit to the patient may outweigh the residual risk. The *sixth* guideline is that although the application of new technologies should benefit a bigger group or population, the individual or specific groups cannot be rejected based on numbers only.

- Technology is an enabler. It can never be developed or applied for experimental reasons only. The ethics of technology development and application is grounded in its service to humanity and not scientific experiment. The development and application of technology are therefore not without borders. Bioprinting to create a superhuman being cannot be accepted. The adage is upheld namely that even if you have the capability to do something, you should not always do it. The side effects of technology development and applications cannot be ignored either. A *seventh* guideline is that technology must create value for humans.
- The application of bioprinting should be subjected to ethical approval by an accredited bioethics committee. Apart from matters such as consent, risk, safety, benefit, potential harm, and consequences, should *value adding* also be considered [8]. The baseline question is what makes this technology different from other applications. In addition, should specific challenges associated with bioprinting also be evaluated. When value adding is considered, the intention is to determine what will be different when this

technology is used. If the answer is not convincing, then this technology should not be used as it can be that this intervention is like interventions already in use. An *eighth* guideline is that new technologies should be an improvement on existing technologies. The improvements can be financial, time to recover, efficiency or sustainability.

- Bioprinting also raises the necessity to engage with other scientific disciplines to reach a decision. For example: If applied technology is viewed as part of the engineering disciplines, then two core values are *safety* and *security*. The high risk of infection is closely associated with bioprinting. Even if the application of this technology may meet all safety standards, then the reality of infection cannot be ignored. Applied to the ethics of bioprinting, then the guideline will be how safe is this technology. It is for this reason that Kesti, Fisch, Pensalfini, Mazza and Zenobi [26] call for the standardisation of bioprinting. They refer to matters such as the bio-ink meeting the requirements for biocompatibility and flow and the effect of process parameters on the mechanical properties of the printed graft. From this they identify guidelines to optimise bioprinting. The importance of these guidelines also differs based on a five-point scale.

In addition, relevant ISO standards can give further guidance on the quality of material and process contributing to the quality of the product. Relevant examples are ISO1348: 2016, Medical devices - Quality management systems: Requirements for regulatory purposes [27] and ISO 10993, Biological evaluation of medical devices [28]. Of special importance is the focus on health and safety as reflected by, amongst others, the South African Occupational and Safety Act 85 of 1993 [29].

What can be observed from these comments is that matters such as the effectiveness of sterilisation and storage also contribute towards the ethical acceptance of this technology. A *ninth* guideline is that bioprinting should comply with safety and security standards – during both manufacturing and implanting.

- The application of biotechnology should not be considered in the context of the lesser of two evils as there is no conflict of interest since alternative applications are available. A conflict of interest requires that a choice be made between two conflicting values. In this case there are no competitive values. The consideration should rather be in the context of the attainability of the situation as the technology is progressing towards improving health and the quality of health. Its application may not be the ideal now, but it steadily progresses towards the improvement and refinement of the technology. The point of these comments is that the ethical call on the desirability of a technology often depends on which perspective is used to evaluate a matter. The integrity of the ethical process and decision-making cannot be ignored. A *tenth* guideline is not to ignore the perspective from where a situation is evaluated.

In summary: Sprinkle [30] comments that additive manufacturing is different from conventional manufacturing processes. He, therefore, argues that “successful use of AM requires a way of thinking that is different from conventional manufacturing.” Based on this advice, four sets of ethical guidelines for decision-making in bioprinting are identified. These sets are:

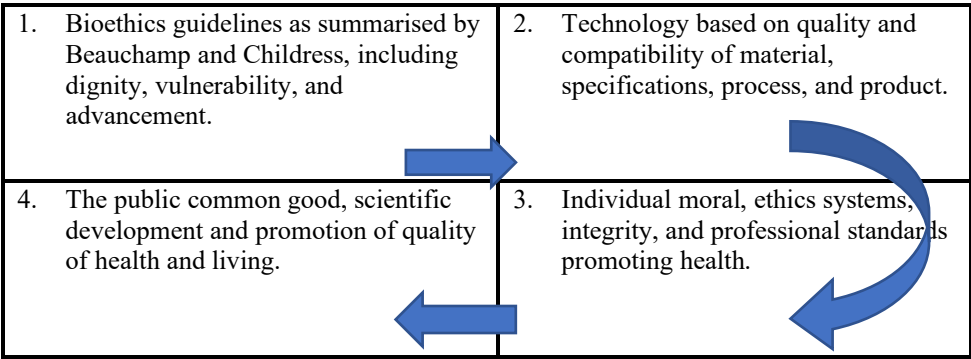


Fig. 1: Ethical decision-making in bioprinting.

These sets should focus on a person-centred ethics within medicine and healthcare.

6. Summary

This paper identifies relevant ethical principles for bioprinting. These principles derive from ethical models and views relevant for experimental research, humans as potential recipients of bioprinting using human cells and tissue.

The research is grounded in the construction of arguments based on concept analysis, bioethics, and the ethics of technology. A multidisciplinary literature review was used. The wider definition of bioprinting includes the layer-by-layer addition of organic material to create a predefined shape.

The paper recommends a broader scope of guidelines next to the acknowledged bioethics principles for bioprinting. The identified guidelines are not intended to judge the ethical acceptability of a project, but rather to guide those considering the ethics of such project.

References

1. J. H. Van den Berg, *Medische macht en medische ethiek*. Nijkerk: Uitgeverij G.F. Callenbach. (1969).

2. Republic of South Africa (RSA), *Report of the Presidential Commission on the Fourth Industrial Revolution*. The Presidency: Republic of South Africa (2020).

3. J. Creplet, *De derde revolutie in de geneeskunde*. Brussel: Pharma.be. (2013).

4. World Economic Forum, *Health and Healthcare in the Fourth Industrial Revolution. Global Future Council on the Future of Health and Healthcare 2016-2018*. Geneve. (2019).
https://www3.weforum.org/docs/WEF_Shaping_the_Future_of_Health_Council_Report.pdf Downloaded from the internet on 26 January 2023.

5. SANDVIK, *What is AM?* <https://www.additive.sandvik/en/about-us/what-is-additive-manufacturing/> (2022). Downloaded from the internet on 12 December 2022.

6. S. Miller, The Billion Cell Construct: Will Three-Dimensional Printing Get Us There? *PLoS Biol* **12**(6): e1001882. (2014). doi:10.1371/journal.pbio.1001882. Downloaded from the internet on 22 September 2023.

7. S. Fanucci, M. W. Barwick, E. Prinsloo. Bioprinting: Prospects, considerations and challenges for application in South African clinical environments. *South African Medical Journal* 2019;**109**(8b):34-39. DOI:10.7196/SAMJ.2019.v109i8b.13838. Downloaded from the internet on 22 September 2023.
8. A.J. Kanter, K.R. Jongsma, M.C. Verhaar, A.L. Bredenoord. The Ethical Implications of Tissue Engineering for Regenerative Purposes: A Systematic Review. *Tissue Eng Part B Rev.* 2023 Apr;**29**(2):167-187. (2023). doi: 10.1089/ten.TEB.2022.0033. Downloaded from the internet on 22 September 2023.
9. ISO/ASTM 52900: 2015, Additive manufacturing: General principles and Terminology. (2015). <https://www.iso.org/obp/ui/#iso:std:iso-astm:52900:dis:ed-2:v1:en>. Downloaded from the internet on 24 June 2023.
10. Wohlers Report 2022, (2022). <https:// Wohlersassociates.com/terminology-and-definitions/additive-manufacturing>. Downloaded from the internet on 14 April 2022.
11. S. Vijayavenkataraman, A perspective on bioprinting ethics. *Artificial Organs.* **40** (11); 1033 – 1038. (2016). <https://doi.org/10.1111/aor.12873> Downloaded from the internet on 13 December 2022.
12. R.C. Rabin, "Doctors Transplant Ear of Human Cells, Made by 3-D Printer". *The New York Times.* (2 June 2022). <https://www.nytimes.com/2022/06/02/health/ear-transplant-3d->. Downloaded from the internet on 13 December 2022.
13. 3D Printing Industry. *3DBio Conducts successful human ear reconstruction with 3D bioprinted Aurinovo Implant.* (6 June 2022). <https://3dprintingindustry.com/news/3dbio-conducts-successful-human-ear-reconstruction-with-3d-bioprinted-aurinovo-implant-210201/>. Downloaded from the internet on 22 September 2023.
14. F. Gilbert, C.D. O'Connell, T. Mladenovska, S. Dodds, Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine. *Sci Eng Ethics.* Feb; **24**(1):73-91. (2018). <https://doi.org/10.1007/s11948-017-9874-6>. Downloaded from the internet on 13 December 2022.
15. N. Vermeulen, G. Haddow, T. Seymour, A. Faulkner-Jones, W. Shu, 3D bioprint me: a socioethical view of bioprinting human organs and tissues. *Journal of Medical Ethics,* **43**:618-624. (2017). [10.1136/medethics-2015-103347](https://doi.org/10.1136/medethics-2015-103347). Downloaded from the internet on 14 December 2022.
16. G. Ogoh, *The ethical issues of Additive Manufacturing.* Unpublished PhD study: De Montfort University. (2020). https://dora.dmu.ac.uk/bitstream/handle/2086/20571/PhD_Thesis_George_Ogoh_October_2020_Final.pdf?sequence=1&isAllowed=y. Downloaded from the internet 29 November 2022.
17. O. Hooper, Five ethical concerns with 3D Printing in Medicine. *Law Technology Today.* (26 May 2020). <https://www.lawtechnologytoday.org/2022/05/five-ethical-concerns-with-3d-printing-in-medicine>. Downloaded from the internet on 12 December 2022.
18. S. Simana, Reflections on Bioprinting Law: How should 3D-Bioprinted organs be classified and what does it mean to treat them as property. *Science. Law and Biosciences Blog.* (12 September 2022). <https://law.stanford.edu/2022/09/12/reflections-on-bioprinting-law-how-should-3d-bioprinted-organs-be-classified-and-what-does-it-mean-to-treat-them-as-property/>. Downloaded from the internet on 12 December 2022.
19. S. Dodds, 3D printing raises ethical issues in medicine. *ABC Science (15 February 2015).* <https://www.abc.net.au/science/articles/2015/02/11/4161675.htm>. Downloaded from the internet on 09 July 2023.
20. A. Kirillova, S. Bushev, A. Abubakirov, G. Sukikh. Bioethical and Legal Issues in 3D Bioprinting. *Int J Bioprint.* Apr **28**;6(3):272. (2020). doi: 10.18063/ijb.v6i3.272. Downloaded from the internet on 13 December 2022.

21. T. Walsh, *Machines behaving badly: The morality of AI*. La Trobe University Press. (2020).
22. T.L. Beauchamp, J.F. Childress, *Principles of biomedical ethics*. 7th edition. New York: Oxford University Press. (2013).
23. B. Varkey, Principles of Clinical Ethics and Their Application to Practice. *Med Princ Pract.* **30**(1):17-28. (2021). [doi: 10.1159/000509119](https://doi.org/10.1159/000509119). Downloaded from the internet on 8 July 2023.
24. B. Taylor, Leadership Just because you can doesn't mean you should. *Harvard Business Review*. (6 December 2011.) <https://hbr.org/2011/12/just-because-you-can-doesnt-me>. Downloaded from the internet on 8 July 2023.
25. A. Zimmerling, X. Chen, Bioprinting for combating infectious diseases. *Bioprinting*. Dec;**20**:e00104. (2020). [doi: 10.1016/j.bprint.2020.e00104](https://doi.org/10.1016/j.bprint.2020.e00104). Downloaded from the internet on 8 July 2023.
26. M. Kesti, P. Fisch, M. Pensalfini, E. Mazza, M. Zenobi. Guidelines for standardization of bioprinting: A systematic study of process parameters and their effect on bioprinted structures. *BioNanoMaterials*. (2016). [17. 10.1515/bnm-2016-0004](https://doi.org/10.1515/bnm-2016-0004). Downloaded from the internet on 8 July 2023.
27. International Organization for Standardization (ISO). ISO 13485: 2016, Medical devices - Quality management systems: Requirements for regulatory purposes. (2016). <https://www.iso.org/files/live/sites/isoorg/files/store/en/PUB100377.pdf> Downloaded from the internet on 22 September 2022.
28. International Organization for Standardization (ISO). ISO 10993-1:2018, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. (2018). <https://www.iso.org/obp/ui/#iso:std:iso:10993:-1:ed-5:v2:en>
29. Republic of South Africa, *South African Occupational and Safety Act 85 of 1993* (1993). https://www.gov.za/sites/default/files/gcis_document/201409/act85of1993.pdf. Downloaded from the internet on 8 July 2023.
30. T. Sprinkle, The 5 most important standards in additive manufacturing. *Standardization News: ASTM International*. (no date) <https://sn.astm.org/features/5-most-important-standards-additive-manufacturing-.html>. Downloaded from the internet on 8 July 2023.