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Responsible and safe innovation in education: an iGEM showcase

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ABSTRACT

This paper showcases a project involved in the international Genetically Engineered Machines (iGEM) competition – a competition dedicated to the advancement of synthetic biology – executed at Delft University of Technology, the Netherlands. Through this case, we illustrate how Value Sensitive Design (VSD) and Safe by Design (SbD) are embedded in education associated with iGEM to arrive at a safe and responsible project design by integrating values and, particularly, the value of safety. As particularly SbD is still quite generally described in literature, we aim to make SbD more tangible to peers, and to inspire other iGEM teams and educators. In addition, we reflect on VSD and SbD in the context of Responsible Research and Innovation and provide guidelines for other iGEM projects to implement VSD and SbD approaches in their designs. To conclude, we explore if, and how SbD and iGEM projects could function as anticipatory governance tools for synthetic biology.

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Uncertain risks; synthetic biology; value sensitive design; safe by design, responsible research and innovation

Introduction

Since Responsible Research and Innovation (RRI) – or Responsible Innovation (RI) – became an essential part of the EU Horizon 2020 research agenda in 2011, the notion has also become more embedded in engineering education (Behm, Culvenor, and Dixon 2014; Deppeler and Aikens 2020; Richter, Hale and Archambault 2018; RIVM, n.d.), alongside with complementary methods such as Value Sensitive Design (VSD) and Safe by Design (SbD). However, what these approaches specifically entail and how they may be applied still remains somewhat general. In this paper, we present a case from the International Genetically Engineering Machines (iGEM) competition – an annual competition for students dedicated to the advancement of synthetic biology to tackle every-day or global problems – to shed light on how students can apply the

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above mentioned approaches and what lessons can be derived for responsible engineering practice.

IGEM is an example of educational organisations that highly regard the notion of RI (iGEM Foundation, n.d.-a; Smolke 2009). The organisation advocates for participating students to develop their projects conforming to RI guidelines and fosters a culture of responsibility and innovation in synthetic biology (Balmer and Bulpin 2013). Elements such as biosafety, biosecurity, ethical considerations, risk assessments and adaptive risk management are underscored by the competition (Millet and Alexanian 2021), which has made iGEM the leading platform for advancing synthetic biology in a safe and responsible way. As the field of synthetic biology is still heavily under development, collaboration and mutual learning between students form a significant part of an iGEM project. Students engaged in iGEM need to see to it that their project has a 'desirable' impact and does not pose risks to the environment, people or animals. This not only calls for application of the RI framework, i.e. anticipation, inclusion, reflexivity and responsiveness (Stilgoe, Owen, and Macnaghten 2013), but also engagement in exploring potential risks and defining strategies to lower or circumvent these (Betten et al. 2018; Stemerding et al. 2019). To accommodate this, we, the authors of this paper, have integrated VSD (van den Hoven 2013) and SbD (Hale, Kirwan, and Kjellén 2007; Kelty 2009) in education for students participating in iGEM at Delft University of Technology (TU Delft), the Netherlands. This way, we provide partaking students with the necessary tools to design a safe and responsible iGEM project.

The first step in the design process is VSD which provides a method to conduct responsible research and innovation by shedding light on moral values (e.g. safety, sustainability, equity, equality, justice) that need to be (proactively) taken into account throughout a design process (Friedman 1996; Friedman et al. 2008, 2013). Following VSD, students zoom in on the value of safety, and apply SbD as a way to identify and anticipate risks associated with emerging applications of synthetic biology (e.g. Asin-Garcia et al. 2020; Robaey et al. 2017; van de Poel and Robaey 2017). The notion has been implemented thoroughly in the field of nanotechnology (Khan and Amyotte 2003; Schwarz-Plaschg, Kallhoff, and Eisenberger 2017; van de Poel and Robaey 2017) and has been gaining foot in synthetic biology (Kapuscinski et al. 2003; Robaey 2018). Although SbD has been extensively described in literature, it is still generally conceived as a broad notion of incorporating safety and responsibility (Bouchaut and Asveld 2020; Gulumian and Cassee 2021; Krouwel et al. 2022; van de Poel and Robaey 2017), thereby differing in terms of suitable strategies for safety per field of application (van Gelder et al. 2021). In that sense, only few reports and publications explicitly describe examples of how SbD strategies have been implemented in synthetic biology. Therefore, the notion stays abstract for stakeholders who want to actively engage with this approach, e.g. researchers, engineers and lecturers.

The goal of this paper is three-fold. First, we want to make SbD more tangible for engineers, researchers and educators, and provide an example of how SbD is operationalised in iGEM education at TU Delft. Hopefully, this can serve as an example to other iGEM teams and inspire peers developing educational material. Secondly, if we zoom out and place VSD and SbD in the context of RI, VSD and SbD seem to differ in terms of focusing on the design process – which also reflects on the position of the researcher in the wider innovation system – while RI takes on a more holistic approach.

This raises questions on what students will take along when they enter a professional environment, and to what extent VSD and SbD are applicable in different contexts than design processes as these approaches seem to pay less attention to institutional social contexts. This raises the question on if, and how SbD and iGEM projects could function as anticipatory governance tools.

Responsible innovation approaches

RI is often put forward as a means focussing on participatory research methods to create more inclusive and sustainable innovations balancing social, cultural and environmental needs, in a pro-active way (Stilgoe, Owen, and Macnaghten 2013). The potential of this forward-looking way of technology development and design has been recognised in several research agendas, e.g. the European Commission's Horizon programs, in which the notion holds a prominent place.

In general, the framework is characterised by three different features (Owen, Macnaghten, and Stilgoe 2012). First, it places more emphasis on research and innovation being ethical, inclusive and democratic, thereby shifting incentives for research from being 'curiosity-driven' to meeting demands from society. Secondly, the approach takes on a more holistic perspective for reflecting on potential impacts of an innovation trajectory, and whom these impacts concern. Third, the notion of responsibility pertains to a broad range of actors, instead of mostly focusing on researchers. In order to achieve the embedded features in RI, four key principles have been developed: anticipation, reflexivity, inclusion and responsiveness (Stilgoe, Owen, and Macnaghten 2013), all with the aim to eventually result in inclusive and responsible technology designs.

RI has been extensively discussed in literature. Some years ago, part of the discussion revolved around whether or not RI was partly developed and embraced in research communities and practices in response to Technology Assessment's shortcomings (Delvenne 2017; van Lente et al. 2017). More recently, discussions have been devoted to RI being founded and further developed mostly in European contexts. For instance, implementing this approach in other contexts such as the Global South seems complex and limited (Hartley et al. 2019; Postal et al. 2020; Wakunuma et al. 2021). Also, the principle of reflexivity within RI has been questioned, particularly regarding public participation and the political domain (Conley and York 2020; Owen, von Schomberg, and Macnaghten 2021). Other criticism is aimed at the applicability and implementation of RI in industry. The approach has a top-down orientation and thereby neglects how actors actually 'do' RI (Jakobsen, Fløysand, and Overton 2019), thereby failing to offer concrete action perspectives to innovators (Sonck et al. 2019). In response, VSD received increased attention as a design approach as it can provide more concrete guidelines to account for human needs and values, and to translate these into technical design requirements (Friedman et al. 2013; van den Hoven 2013).

Value sensitive design

VSD has originated from the fields of social sciences, the humanities and computer science. In the latter discipline, VSD was used to develop and design computer technologies, thereby considering social consequences as well as ethical norms, e.g. privacy, security. The idea is that moral values can already be taken into account pro-actively in technology development by means of three different 'VSD' stages.

The first stage, the conceptual investigation, entails the identification of relevant stakeholders (direct and indirect) within the design process. This step does not limit itself to solely determining who the affected stakeholders are and what values they consider to be of importance but also tries to engage itself within trade-offs of competing values (Friedman et al. 2013; van de Poel 2013). An advantage of the conceptual investigation is that it clarifies any issues or conflicts (e.g. between values or stakeholders) and forms a basis for comparison (Friedman et al. 2013; Miller et al. 2007). The second step within this process is to investigate empirically how earlier identified values are being applied to human contexts. This can be done by conducting interviews or surveys, but also by performing observations (van de Poel 2013). The third step, the technical investigation, aims to translate earlier identified values and empirical data into tangible design requirements. However, this last step is usually conducted in two forms: one focusing on how existing technological properties support or may hinder human values, and one focusing on how the design can support values. Although the empirical and technical investigations seem to overlap, what must be clear is that the technical investigation focuses solely on technology, while the empirical step also includes social factors. A matter of importance during these steps is that one should not get stuck in a moral overload; where one is burdened by conflicting obligations or values that hold the same hierarchy, but cannot be realised at the same time (van den Hoven 2013). A more elaborate explanation of the performed VSD analysis is provided in the Section 'VSD and SbD in Practice: PHOCUS – Target locusts from within'.

Safe by design

Literature suggests that if we can design for a range of values, like with VSD, we can also specifically design for the value of safety (Fahlquist, Doorn, and van de Poel 2015; van de Poel and Robaey 2017). Along that line, SbD is phrased as a risk management approach that focuses on safety by encouraging actors involved in the design process of a technology (i.e. researchers, engineers) to take responsibility for future safety during the idea and design phase of a technology by providing anticipatory strategies to prevent or mitigate emerging risks (Fahlquist, Doorn, and van de Poel 2015; Robaey 2018).

Recently, Safe and Sustainable by Design (SSbD) – which also focuses on the value of sustainability in addition to safety – has been adopted by the European Commission. In 2022, the approach was put forward in the Chemical Strategy for Sustainability, part of the European Green Deal as a way to phase out harmful chemicals and to develop safer, more sustainable compounds (Caldeira et al. 2022; European Commission 2020). The prominent role of SSbD in this strategy's research agenda is partly due to positive outputs of SbD in other fields. The approach has been implemented thoroughly in the fields of nanotechnology (Khan and Amyotte 2003; Schwarz-Plaschg, Kallhoff, and Eisenberger 2017), biotechnology and synthetic biology (Asin-Garcia et al. 2020; Kapuscinski et al. 2003; Robaey 2018). As these fields are considered emerging fields, there can be insufficient knowledge in terms of the technology itself or the eventual application, which calls for an iterative process in which emerging risks and/or uncertainties can be anticipated or lowered – which is the goal of SbD. In that sense, SbD can be used as a way to discover what new risks associated with emerging synthetic biology applications may entail (e.g. ‘practicing in the lab’) and, through that, function as an anticipatory governance tool (Guston 2013). Particularly the iterative character and focus on ‘active’ or controlled learning, i.e. putting designated procedures in place for learning about potential risks, can be a way for responsible risk management and dynamic governance, and to give direction to the further development of the field (Guston 2013; Guston and Sarewitz 2002; van de Poel 2017).

However, applying SbD, or using SbD as a tool for anticipatory governance in the field of synthetic biology is no guarantee that new innovations or technologies are indeed safe or sustainable, nor that we will arrive at future-proof governance and regulation. Nevertheless, when more attention and awareness are devoted to the notion of safety, this will potentially lead to a safer industry and safer products and processes. Additionally, active stakeholder involvement, active communication, and transparency between stakeholders about optional design choices and potential risks and uncertainties would be crucial, but this also raises the question of whom to engage. As with any innovations, some issues may only be discovered when the technology already finds itself at a later stage of development (e.g. during upscaling or after market introduction) when initially excluded stakeholders start to make use of this innovation (Collingridge 1982). Or it may only later become clear that certain design choices that initially led to increased safety conflict with other values. For example, the value of safety could lead to a value conflict with e.g. sustainability in a later stage of development (Bouchaut et al. 2021). Also, other matters related to security, e.g. privacy issues or dual-use (Millett et al. 2020; Vennis et al. 2021) might call for a different choice of design in which safety is still ensured but no conflict emerges with another value. Coming to an ‘optimal design’ calls for value trade-offs which is challenging, particularly when a technology is still in pilot stages of development and the potential risks (and benefits) are uncertain (Bouchaut and Asveld 2021).

Safe and responsible innovation in iGEM

In iGEM, students work on innovative research projects, and so contribute to the advancement of synthetic biology. The notion of RI is embedded in every component of the competition, as the success of an iGEM project is largely determined by its ethical, social, and legal context. For instance, students must pay considerate attention to (bio)safety and (bio)security, e.g. dual-use, ethics, and the social impact of their projects by means of stakeholder interaction, and education and outreach (Kelwick et al. 2015). These latter aspects are referred to as ‘Human Practices (HP)’, which form an integral part of the iGEM competition and encourage teams to reflect on the broader consequences of their work in synthetic biology (Rabinow and Bennett 2012).

Safety and biosecurity in synthetic biology are considered of utmost importance globally (Donati et al. 2022; Rerimassie et al. 2015), and are thus also highly regarded within iGEM. This strong focus on safety and security could be considered as too narrow, given the many other relevant societal issues such as economic justice and sustainability. However, because safety and security are such well known values within the community, they also offer an entrance to bring in wider issues within the iGEM community. The methods of VSD and SbD urge practitioners to take a wide range of stakeholders and values into account. These design-oriented approaches furthermore provide students with actionable tools to respond to identified societal issues. This is much less the case if they would be asked to tackle systemic injustices resulting from the current economic structures. Although it is desirable that students are aware of such wider issues, it is most empowering for them to be able to address values directly through design.

Synthetic biology offers ample tools to deal with safety and security. Although it is considered a relatively new field, there is already over a decade of experience in terms of safety and (bio)security (Millett et al. 2020). For instance, within iGEM, an expert committee on safety and security is appointed that provides advice to student teams, e.g. on performing risk assessments. Also, students have to demonstrate to the expert committee that they are working safely (i.e. adhere to safety rules, proper lab training), adhere to rules and policies (i.e. projects may not be tested or released outside the laboratory – only contained use), and teams have to proactively mitigate potential risks that may arise during their projects (iGEM Foundation 2021). Given that each year more than 6000 student teams partake in this competition, this provides valuable information on the emergence of new types of risks given the innovative nature of many student projects. This data is used to identify new risks and to develop risk management strategies to lower or anticipate these, or to eventually determine thresholds for what would be considered acceptably safe and under which circumstances (Millett et al. 2019), which can again serve for anticipatory governance, adapting or improving policy and risk management and directing the emerging field (Millet and Alexanian 2021). So in a way, the iGEM environment can function as a 'testing ground' for governance to identify gaps and develop modifications (Kuiken 2020; Weiss Evans et al. 2020).

Anticipatory governance in synthetic biology

An example of such 'testing ground' is the many iGEM teams that have been working on gene drives. These teams have generated valuable information – technical, societal and ethical aspects – for risk managers and policymakers to work on developing future governance (Millett et al. 2022). Such projects provide insights into safety, security and respective governance, but they also give rise to questions revolving around the future of biology in general, responsibilities pertaining to synthetic biologists (Frow and Calvert 2013), IP and patenting, and fundamental questions on 'naturalness' and 'what is life?'. Key discussions revolve around whether synthetic biology 'constructions' such as synthetic genomes or protocells can still be considered 'natural,' or whether these should be labelled as artificial, or whether these should become a new category within 'life' (Bedau et al. 2009; Calvert 2010). Also, the patenting of applications that make use of naturally occurring genomic sequences or digital sequencing raises questions on ownership and accessibility (Bagley 2016; Bruynseels 2020; Kreiken and Arts 2024).

While the emerging regulatory regime around gene drives presents a more recent example of anticipatory governance in synthetic biology (Kuzma et al. 2018), the idea of managing emerging technologies goes back some years to the time that nanotechnology was upcoming (Guston 2008). Despite its promises, the notion has been criticised on some pitfalls, for instance, the complexity and unpredictability of forecasting future developments and, subsequently, difficulties in foreseeing potential risks, benefits, and societal implications. As a result, both potential risks and benefits are often exaggerated, and emphasis is overly placed on risks and safety, stifling innovation. Furthermore, the upstream engagement of researchers (and thus dependency) contributes to a linear innovation trajectory, and public engagement often more resembles ‘making the public ready’ (Delgado, Kjølberg, and Wickson 2010).

Nevertheless, when these pitfalls are taken into account, anticipatory governance offers a promising approach to managing uncertain risks associated with emerging technologies and thus, it has been applied over the years to, e.g. artificial intelligence (Aicardi et al. 2018), in the light of climate change (Gupta et al. 2020; Muiderman et al. 2020; Quay 2010), biomedical advancements (Fisher et al. 2014; Rueda et al. 2024; Rychnovská 2021) and, thus, synthetic biology (Ribeiro and Shapira 2019; Stemerding et al. 2019). For this latter field, iGEM forms an excellent nesting ground for new applications of synthetic biology, and thus it could be eminently suited to use anticipatory governance. Of course, using iGEM projects as a means for anticipatory governance also comes with challenges, on which we elaborate in the Discussion’s subsection ‘iGEM as anticipatory governance instrument’.

IGEM at TU Delft

While mostly engineering students partake in this competition, iGEM emphasises the multidisciplinary approach that is needed to arrive at responsible and safe project designs. Besides technical features, also matters related to ethics and social responsibility, science communication and public outreach, and examining relevant policy, regulation and law are of utmost importance (iGEM Foundation, n.d.-b; Millett et al. 2022; Stemerding et al. 2019). It is crucial that students become aware of this interrelatedness at the start of their project as certain design choices may appear very desirable in a technical sense (e.g. high efficiency or accuracy) but can give rise to an emerging risk or bottleneck coming from a different angle. For example, when implemented outside the controlled environment of a laboratory[1], a genetically modified organism or certain type of genetic modification could lead to undesirable competition with a local ecosystem, gene transfer, or could simply turn out to be undesirable from a (local) societal perspective. To ensure that iGEM projects are being developed in a safe and responsible way, also at TU Delft, we have taken on a multidisciplinary approach in which the notion of RI forms an integral part of associated education.

To provide students guidelines to identify values, set up norms and design requirements, and anticipate uncertain risks during the development of their project, both VSD and SbD are used to operationalise RI. Figure 1 is a schematic overview (four-diamond model) of the first idea stage, VSD, SbD and a general reflection on the entire process by means of the RI principles that are guiding in the design process of an iGEM project at TU Delft.

Design process

The design process starts with identifying a range of problems that the students are interested in tackling in their iGEM project; phase 0. Divergent thinking is applied to list current problems for which a synthetic biology application could be applied. After

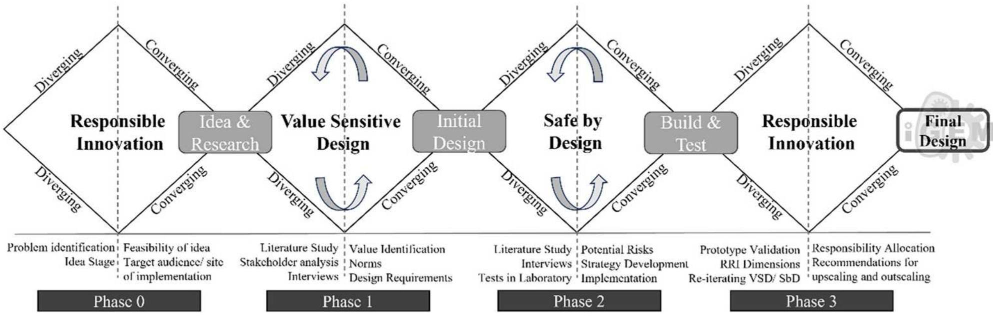

Figure 1. Four-diamond model illustrating an iGEM project's iterative design process within TU Delft, consisting of three stages: (0) Initial idea phase, problem identification and feasibility of idea, (1) Value Sensitive Design, (2) Safe by Design, and (3) Reflecting on Responsible Innovation. Of course, these steps are not a linear process and provide room for multiple iterations until the final design is obtained.

this, students list the defined problems according to their own preference and in terms of feasibility as they only have 8 months to conduct an iGEM project. Once decided on the problem and approaches on how to tackle this, a proposed site of implementation is chosen for the next phases, the VSD and SbD.

The first phase, VSD, sheds light on relevant moral values that must be considered by students during the development of their project. Divergent thinking is initially used for the conceptual investigation to gain more insights into the broader context of their project by using literature, mapping stakeholders and determining which are the most powerful or influential using a power-interest grid, and conducting interviews. Based on all derived information, convergent thinking is applied for the empirical investigation where insights from all interviews and literature are combined. This sheds light on relevant values and possible value-conflicts (e.g. privacy and reliability of data), and provides insight into which values are met, which are not, and which are difficult to translate to norms and design requirements. For instance, values related to notions such as 'respect' or 'integrity' are mostly dependent on human behaviour and are therefore difficult to translate into tangible design choices. After the first phase, students have acquired important data and information on what values to prioritise in their design choices and to what value conflicts this could lead. By means of a value hierarchy (i.e. which values to prioritise over others?) students can analyse where there is room for improvement in their initial design idea and establish norms and formulate technical design requirements for this (Friedman et al. 2008; van de Poel 2013, 2015). Also, if felt that information is lacking, students may re-iterate steps within this first phase.

Keeping the identified design requirements and potential value conflicts in mind, students zoom in on the value of safety and transfer to the second phase; SbD. In this stage, first, students apply divergent thinking again by means of literature and interviews to explore what issues may arise. These can be technical risks, but also uncertainties related to societal implications of which we lack knowledge and understanding. Insights of such kind can be derived from e.g. interviews with associated stakeholders, results from lab experiments or modelling. In response, anticipatory or risk-reducing strategies are developed which must be fed back in the design of the project and may result in an alternative design choice to ensure safety. Also, it is analysed which strategy or strategies would be most beneficial to be implemented in terms of technical and societal aspects, and to what extent earlier identified value conflicts emerge. This may again call for iterations within the first or second design phase and may result in not all earlier design requirements being met.

While portrayed as 'separate' steps within Figure 1, phases 0 and 3 are also embedded within the first and second step of the design process, i.e. VSD and SbD, as students continuously reflect on their findings and design choices – hence the iterative character of the design process. When the (close to) final design becomes clear, students perform a general reflection on their findings to find any shortcomings, knowledge gaps or other matters that are not (sufficiently) being met in the choice of design and may call for additional research. Inherent to this reflection are the RI key characteristics that guide students in applying a holistic perspective to their project.

For anticipation, this would involve questions on whether all potential impacts have been considered and anticipated accordingly. Also, for what other purposes the project could be used, and what measures should be taken to facilitate or prevent this? Reflexivity would call for questions posed on how certain assumptions and beliefs may have influenced the design process. What was missed? What are the limitations of the designed project? In terms of inclusion – and related to reflexivity – students assess if certain stakeholders have been missed in the project. For instance, when the project has reached its final design stage, some implication strategies may have changed which would call for alternative stakeholders to be consulted. Lastly, students evaluate on how responsive their design is. Related to safety aspects, this could entail an unexpected issue arising and the potential of making changes to the design to accommodate for this issue, or to completely cancel the technology (e.g. a kill-switch). As a result of the divergent thinking and reflecting on the design process with RI, students formulate recommendations on knowledge gaps, stakeholder involvement and in terms of assigning responsibilities to certain stakeholders – e.g. who is responsible to make sure that something is or is not happening? This also applies to (the hypothetical) up-and-outscaling of their designed project.

While Figure 1 may seem to illustrate a fairly linear innovation process, the development of an iGEM project never is. Issues, potential risks or tensions between values or stakeholders may emerge anywhere in the process, and call for many iterations within the process. Therefore, the multidisciplinary character is continuously emphasised, making students aware that all their separate work and data from e.g. the lab, stakeholder consultation, risk assessments and modelling, feeds into their colleagues' and therefore working and discussing findings and results collectively is strongly encouraged.

In the next section, we will elaborate on how Figure 1 is put into practice by showcasing the TU Delft 2020 iGEM project 'PHOCUS', focusing on phase 1 and 2. Below, we will first shortly illustrate the conducted VSD analysis and derived values, norms and design requirements. Then we continue with SbD and present the identified potential issues and risks, and the implemented SbD strategies. Lastly, a reflection on the design process, VSD and SbD is provided. For transparency, the work described below is the iGEM students' work – the authors have acted as supervisors by providing regular feedback and guiding them throughout their project.

VSD and SbD in Practice: PHOCUS – 'Target locusts from within'

The students that developed the 2020 iGEM 'PHOCUS' project aimed to tackle locust swarms caused by gregarious-state desert locusts (*Schistocera gregaria*) by using genetically modified bacteriophages that secrete a toxin in the locust's gut – thereby killing the locusts 'from within'. We have explicitly chosen for this case to be examined more closely as it can be regarded as an instrumental case that sheds light on multiple aspects that need to be taken into account to arrive at a safe and responsible innovation (Crowe et al. 2011; Stake 1995). First of all, 'PHOCUS' makes use of state-of-art-technology and, in that regard, covers aspects related to fundamental research – which is crucial to cover in academic training and education and illustrative for the vastly developing field of synthetic biology. Secondly, the envisioned site of implementation, including the wide range of associated stakeholders, provides insights into the case's societal and regulatory context, which also needs to be taken into account in the final design of PHOCUS. Thirdly, the PHOCUS case sheds light on newly emerging risks (e.g. horizontal gene transfer, bioaccumulation and potential disruption of local ecosystems), and aspects related to societal implications, IP and ownership (accessibility and affordability for vulnerable groups of people). Regarding this case as an instrumental case study allows us to identify aspects related to responsible innovation and safety more generally and so to generate findings that can be transferred to other similar cases, and thus being better applicable to other iGEM projects.

Value sensitive design

The first step in the students' design process was to conduct a VSD analysis to identify relevant stakeholders and derive their most important values. Based on this first analysis, norms and design requirements were formulated that formed the starting point for the development of PHOCUS. As iGEM projects are developed in contained settings and not introduced in the 'real world', hypothetical scenarios are used (e.g. a specific context or site of implementation). To also keep the number of associated stakeholders in their analyses realistic, students choose a specific country (in this case Kenya) that functioned as a pilot site for the hypothetical implementation of PHOCUS. Below, we now give a summary of the conducted VSD analysis. A more detailed overview is provided in Appendix A: Table A1 and Table A2. Table A1 provides the listed identified stakeholders in order of priority (i.e. using a power/interest grid) and their associated values. Table A2 gives an overview of the selected values, the derived norms and design requirements.

As the proposed site of implementation was Kenya, and PHOCUS is a technology that directly affects farmers and local ecosystems, the most important identified stakeholder was the Ministry of Agriculture, Livestock, Fisheries and Irrigation of Kenya. Also, as PHOCUS provides a way to eradicate harmful locust swarms to prevent crops from being destroyed, several stakeholders were considered of great importance too: the Food and Agriculture Organisation, the Desert Locust Control Organisation East Africa, and of course, Kenyan farmers and herdsmen. Additionally, stakeholders were identified that might be competitors for PHOCUS (i.e. chemical companies currently producing pesticides), and the iGEM Foundation itself.

Secondly, associated values were derived from the list of associated stakeholders. This list contains universal values such as ‘equality’ and ‘health’, but also other identified matters that stakeholders find important such as ‘family’, ‘cooperation’. ‘innovation’ and ‘passion’. As these latter matters of importance do not translate directly to values it was sometimes difficult to derive tangible design requirements. Therefore, these were mostly omitted from the third step, the technical investigation, but were taken into account in other design choices, e.g. the location of production, or further retail pathways if the product were to be commercialised. In addition, where possible these other matters of importance were taken into account during the composition of norms and design requirements of other values. For instance, although ‘Respect’ or ‘Honesty’ are difficult to translate to norms and requirements for design, these were considered with ‘Accessibility’ and ‘Equity’.

The technical investigation included values such as ‘Health’, ‘Food Safety’, ‘Accessibility’ and ‘Environmental Safety’ but a more detailed overview can be found in Table A1. Here, we shortly address two (one related to technical aspects, and one to social aspects) and explain what norms and design requirements were derived from these. For example, in response to the value of ‘Health’, the derived norm was ‘No effects on physical or mental health’ for all people (or animals involved, except for the locusts). To adhere to this norm, the following (technical) design requirements were established: (1) Using bacteriophages as genetic carriers as this type of virus is only able to infect a very specific bacterial genus or strain and thus cannot cause infections in humans, (2) No delivery of bacteriophages under acidic conditions to reduce the risk of bacteriophages entering human intestines as the digestive system of locusts is far less acidic than the human stomach, (3) Use a non-toxic, non-pathogenic host microorganism that is not present in humans to reduce the risk of infecting human gut bacteria, or prevent depletion of beneficial bacteria, and (4) The produced toxin must be non-pathogenic to humans and degradable in the human digestive system. In addition, a concern that was strongly discussed during the design stage of PHOCUS was the generation (and release) of a GMO. To reduce the risk of potential recombination of the heterologous DNA in the genome of the bacteriophage with the host genome, a non-toxic and non-pathogenic host microorganism should be chosen, for instance, a lytic phage. This way, the integration of the DNA into the bacterial genome can be avoided as the host will be lysed after viral replication.

In response to the value of ‘Accessibility’, the following norms were constructed (see also Table A2): (1) Access to the product (i.e. PHOCUS) at all times, and (2) Access to knowledge about the product. In line with these norms, the following design requirements were established: (1) There needs to be a robust distribution network, (2) Local production, (3) Affordable, (4) Simple and easy to use, and (5) Sufficient knowledge should be provided to end-users for them to make an educated decision to use, or not use, our product. The argumentation behind these requirements is that to make adequate quantities of food available to people in the affected area(s), PHOCUS must reach local farmers and landowners. Therefore, a robust distribution network should be set up, but to limit the dependence on such large channels, production sites should be developed locally. That way, the product can reach the customers faster and with fewer intermediates. Also, the economic capacity of local stakeholders (i.e. farmers and land workers) must be taken into account. As most countries that are being affected by locust swarms show low mean income, PHOCUS should be as inexpensive as possible. Lastly, although levels of education differ per country, a sufficient level of information should be provided to the potential users of PHOCUS, enabling them to make an informed decision about whether to use, or not use PHOCUS.

After the third step in VSD, the technical investigation, some value conflicts and other tensions between norms and design requirements were encountered. These were, for example, Food Security vs. Environmental Health and Food Safety, and Accessibility vs. Responsibility and Integrity. In response, this had some implications for the technical design options within the project, such as whether to go for a lytic or lysogenic cycle of the bacteriophage, if a kill-switch should be added, whether locusts should be sprayed directly with the bacteriophages or the crops instead, or whether the locusts should indeed be killed or could be prevented from swarming above all? These questions were considered from a SbD perspective and anticipatory strategies were developed to ensure safe and responsible development of PHOCUS.

Safe by design

The identification of uncertain risks or possible issues concerning the biopesticide PHOCUS and the development of anticipatory strategies was achieved through several interviews with technical experts, (bio)ethicists and local stakeholders, extensive literature reviews, and feedback from the Dutch National Institute for Public Health and the Environment (in Dutch: RIVM) which has extensive knowledge on SbD and biosafety & security (RIVM, n.d.). Figure 2 illustrates a selection of the SbD measures that have been considered during the design of PHOCUS (TU Delft iGEM PHOCUS 2020), on which we elaborate below.

Bacteriophage: As previously mentioned, a potential issue that needed to be circumvented is that engineered bacteriophages might be dangerous to humans. However, based on interviews with experts in the field and literature, this risk turned out to be negligible due to bacteriophages not being able to infect human cells (Kutter and

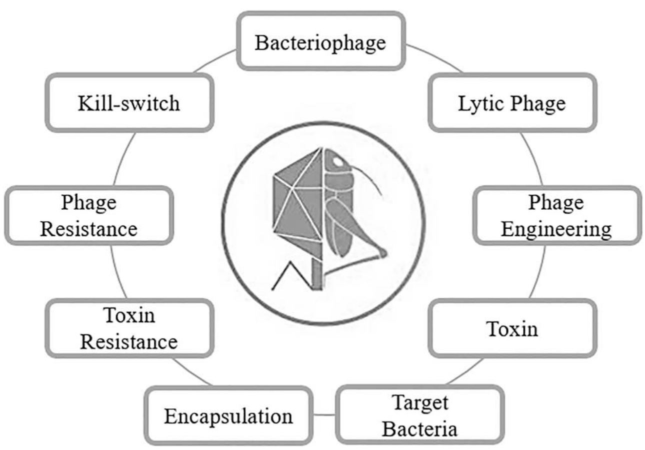

Figure 2. Schematic overview of SbD measures considered for the design of PHOCUS. Adapted from TU Delft iGEM PHOCUS 2020.

Sulakvelidze 2004). Also, the bacteriophage needed to be stable in the locust gut (pH 7-8), meaning that if they would be swallowed by humans, they wouldn't survive in the acidic environment of the human stomach (i.e. pH 1-2) (Evans et al. 1988; Ganeshan and Hosseinidoust 2019; Ventura et al. 2011). Still, the intended type of bacteriophage could be dangerous to animals or other insects besides the locusts (De Paepe et al. 2014). Although studies have been conducted in terms of the influence of bacteriophages on animal microbiota, the impact is not yet well understood. Therefore, more research needed to be conducted, which called for an iteration in the design process. Lastly, it was deemed crucial that the bacteriophages would not remain for long when being released in nature. However, this issue turned out to be negligible as bacteriophages turn out to become unstable when exposed to levels of UV (i.e. sunlight) (Iriarte et al. 2007). Still, to gain certainty about whether the potential issues would be indeed negligible, more data on these issues would have to be collected before PHOCUS would even be admissible for field trials.

Lytic Bacteriophages: One of the questions that arose from the VSD analysis was whether to go for the lytic or lysogenic cycle of a bacteriophage. Based on extensive literature review, PHOCUS decided on using a lytic bacteriophage as it will minimise the risk of horizontal gene transfer and/or phage mediated transduction (Paul and Jiang 2001; Soucy et al. 2015; Verheust et al. 2010; Yutin 2013). Also, the lytic cycle ends with cell lysis, thus cell death that reduces the risk of creating a new GMO. And bacteriophages that reach their target bacteria will propagate quickly due to properties of the lytic cycle.

Bacteriophage Engineering: Engineered bacteriophages led to several concerns: (1) Phage dissemination into the environment, (2) Production of harmful proteins, and (3) Persistence of the applied mutation in nature. Based on literature, several design choices were made to mitigate these potential issues (Nobrega et al. 2016; Verheust et al. 2010). Firstly, the bacteriophage should be engineered with a naturally narrow host range, so the propagation chance of the bacteriophage outside the locust is reduced. Secondly, no potentially harmful sequences for humans, animals or the environment should be inserted in the bacteriophage. And lastly, to examine the stability of the mutation in the engineered genes, the engineered bacteriophage should be propagated in its host for several generations, where after the presence of the mutation can be confirmed (or not) by PCR after each generation. If this is confirmed, this would mean that the insert is extremely stable and thus the mutation could spread through multiple genetic populations. In response, appropriate measures should be taken.

Toxin: Literature described the Cry toxin Cry7Ca1 to be effective against locusts of the species *Locusta migratoria manilensis* by puncturing the gut lining (Song et al. 2008; Wu et al. 2011). Also, Cry toxins turn out to be highly specific to their target insects and therefore only kill a limited number of species (within the locust range of species) (Pardo-Lopez, Soberon, and Bravo 2013). Also, the specificity of the Cry toxins is provided by the mid-gut environment of the insect (Nester et al. 2002). Recalling that humans do not have the same gut conditions as insects (e.g. pH), this toxin should not affect humans when ingested.

Target Bacteria: Bacteria present in the locust gut must be targeted specifically by the bacteriophage. As the locust gut contains multiple bacterial species (*Enterobacter*), PHOCUS must contain a cocktail of bacteriophages that specifically target the bacteria. However, the species *Enterobacter* can also be present in the human microbiome giving rise to the risk of PHOCUS infecting human's bacteria. But, interviews with technical experts and literature review revealed that this risk might be very small as, as mentioned before, the pH in the human stomach is much more acidic compared to the pH in the locusts gut (Zelasko et al. 2017), the bacteriophages are equipped with non-pathogenic bacteria, and the Cry toxin is highly specific to locusts. Nonetheless, more knowledge should be gained through studies on different gut microbiomes.

Encapsulation: Encapsulation acts as a physical barrier to control the environment of a single molecule, thereby preventing off-target infection. For PHOCUS, a physical barrier would've been needed to avoid ecological imbalances in vegetation the bacteriophages are sprayed upon. However, interviews, literature studies and research performed by the students did not result in finding an appropriate encapsulation method (Hof et al. 2002; Jha et al. 2011).

Toxin Resistance: When exposed to (bio)pesticides for a long time, locusts can become resistant as they have slightly varying genetic alterations, of which the strongest (thus being resistant) are being passed on to offspring. For the Cry7Ca1 toxin, locusts ultimately becoming resistant is very likely as a large number of locusts is being exposed to the Cry toxin, and they reproduce quickly. Therefore, the genomes of the locusts should be monitored closely. An anticipatory strategy was developed to only spray PHOCUS in particular areas (Jutsum et al. 1998), or by developing a novel toxin with a different mode of action. Still, more research would be needed to ensure safety in this regard.

Phage Resistance: Not only locusts can develop resistance to PHOCUS, but gut bacteria can too. This will result in no toxins being produced and the locusts not being killed. However, as PHOCUS makes use of lytic bacteriophages, all target bacteria are lysed and therefore resistance development is limited. Still, the students developed a mathematical model (*Team:TUDelft/Model/Toxin Production - 2020.Igem.Org*, n.d.) that predicts the development of resistant bacteria and showed that the selected bacteriophage would kill the entire bacterial population (i.e. *Enterobacter*) within hours. Due to this short timeframe, the bacteria would not be able to develop resistance to PHOCUS.

Kill-switch: A kill-switch could be built in to terminate the engineered bacteriophages might they propagate in nature (Robaey 2018). However, building in such a biocontainment measure was deemed unnecessary as the engineered bacteriophages would decrease naturally over time (Schmerer et al. 2014). That is because PHOCUS depends on a selective advantage over the wildtype and would therefore lose competition with the wildtype bacteriophage. Also, the genetic inserts would be lost over time and the bacteriophage would turn back to its wildtype sequence. In addition, and as mentioned earlier, the engineered bacteriophages become unstable due to exposure to UV and high temperatures (Jończyk et al. 2011), and the lytic nature of the bacteriophage functions as self-limiting (Clark and March 2006; Ul Haq et al. 2012).

General reflection

Unfortunately, often there is no 'optimal design' that can meet *all* identified values, design requirements and issues for safety; this always calls for a trade-off and additional risk-research being set up to gain knowledge on potential risks. In addition, as the iGEM project was developed in a contained setting and not introduced in the 'real world', shortcomings or knowledge gaps could have been missed. Nevertheless, by means of VSD, SbD and the inherent reflection using the RI characteristics, PHOCUS has come up with a list of safety issues that need to be studied more thoroughly before commercialisation and implementation can take place at all. More data should be gathered from laboratory experiments focusing on:

- PHOCUS' toxicity to non-target organisms;
- The pathogenicity to non-target organisms;
- The stability and potential to accumulate in humans and animals;
- The uniqueness of sequence targeted;
- The potential gene flow of insert;
- The specificity of PHOCUS on locusts;
- The stability of bacteriophages in environments no cooler than 20 °C;
- The possibility and extent of pesticide resistance if PHOCUS would be used extensively.

In addition, as PHOCUS makes use of genetically modified (GM) bacteriophages, more stakeholder consultations should be organised. Of course, these should be conducted with local farmers at the intended area of implementation to see if and what objections they may have on using PHOCUS. While VSD already showed that affordability and accessibility are important matters that need to be considered for this group of actors, certain cultural matters, beliefs or practices could be of importance to enable a successful rollout of the product. Also, if PHOCUS would be introduced in other regions or countries, consultations with local stakeholders would be needed again. In addition, ideally, consultations should also be conducted with NGOs advocating against usage of GM. Unfortunately, while students repeatedly reached out to many large environmental organisations, none of them wanted to discuss the impact of chemical pesticides nor their perception on PHOCUS. Lastly, if implemented, PHOCUS could become a competitor to companies in the agrochemical industry that produce pesticides. However, during the development process of PHOCUS, students have reached out to several companies who were generally enthusiastic about the ideas to develop a new biopesticide and would have been open to explore collaborations, which sounds promising.

Discussion

VSD and SbD in iGEM

As mentioned earlier, engineering students may face difficulty in operationalising notions of RI in their practices as this concept often remains quite general in the literature. To make the RI approach more tangible, we have embedded tools to 'do' RI in education; VSD and SbD. The main value of VSD and SbD is to make students more aware of various aspects of safety and moral values and teach them to balance different values against each other. This serves as a counter measure towards the over emphasis on efficiency and profitability they are trained for in other parts of their curriculum.

Along that line, VSD and SbD should ideally be conducted in a complementary way to have a more holistic approach to responsible designs. However, depending on the goal, one could also only do VSD thereby keeping the design requirements more general. If the goal would be safety, then SbD should be conducted more prominently but a VSD analysis should always precede. If not, one cannot gain insights into potential value conflicts with safety other than technical ones, and what a responsible value trade-off should be.

While both VSD and SbD are helpful to arrive at responsible innovations, they also have their flaws. As with VSD, also SbD does not provide a clear methodology for identifying stakeholders (Manders-Huits 2011). While students do reflect on this with the RI characteristics, there is still the chance that important actors have been missed. This also pertains to the lack of complementary ethical theory for dealing with value trade-offs and figuring out the 'right' decision. The main value of these approaches lies in the creation of awareness and a more broadly conceived sense of responsibility amongst engineering students.

VSD and SbD in relation to RI

However, while this iGEM project illustrates that applying both approaches can result in responsible inclusive designs, the methods are very time-consuming to do well, and are, as of yet, not well embedded within industry – as is the case with RI. This raises the question of whether the students will be able to take these approaches along in their further professional careers. Both VSD and SbD focus mostly on the design of an innovation – which would fit their future work – but the general idea behind RI (i.e. responsible innovations taking into account complex institutional social contexts) might not be acknowledged because it relates to commercial strategies and industrial priority setting which are not the main responsibility of a companies' R&D department.

The latter also pertains to responsibility allocation, particularly forward-looking responsibility. As both VSD and SbD are heavily process-focused, responsibility for safety is put on researchers and engineers to a great extent. However, as those actors often only have little say in decision-making processes in industry, this high degree of responsibility does not seem fair. On the other hand, referring to Figure 1, if researchers and engineers would be working solely in phases 1 and 2, and phases 0 and 3 were conducted by those involved in decision-making, then the degree of responsibility may be less problematic. However, for this, excellent communication, information exchange and transparency would be crucial between those stakeholders (Sonck et al. 2017). Not only to allow for iterations between all phases, but also to eventually be able to make the necessary decisions to arrive at responsible designs. Last but certainly not least, industry should place the notion of responsible innovation above other intrinsic values such as profitability, which is contrary to the current capitalistic logic in many industries (Whyte 2020).

IGEM as an anticipatory governance instrument

Although iGEM could be considered a testing ground for fully-fledged anticipatory governance, its potential contribution should not be overrated. iGEM can be an excellent tool to inspire new strategies for risk management, but truly effective anticipatory governance requires the involvement of a wide range of actors as well as a balanced distribution of responsibilities.

First of all, iGEM lends itself well for the identification of risks and uncertainties under normal use by means of VSD and SbD, but this is much more difficult for potential security aspects. Dual use can be hard to eradicate through design because of the extreme scenarios that accompany possible misuse. Security issues, hence, require a more all-encompassing approach, including also policymakers and other regulatory agents.

Secondly, we already mentioned that the responsibilities associated with responsible innovations are forward-looking, and are mostly placed on researchers and engineers. Within iGEM, this would mean that these responsibilities are put on students; they identify potential stakeholders and conduct interviews. In the light of generating information usable as input for anticipatory governance, it is debatable whether this is something desirable. Additionally, responsibilities being placed on researchers and engineers adds to the often bottom-up approach that is embedded in anticipatory governance, risking the continuation of linear innovation and risk governance processes while dynamic ones would be more desirable in the light of the goal of anticipatory governance.

Thirdly, in comparison to, e.g. EU Horizon projects or EC Flagships, iGEM projects are short in time and rather small. In that regard, these projects only provide very limited information and knowledge to be used for future governance. However, of course, these projects can initiate larger project proposals and collaborations or give momentum to other developments. In that case, collected information on the technical, ethical, social, and legal context within iGEM may provide a good starting point for researchers engaged in anticipatory governance.

Lastly, anticipatory governance sometimes fails due to the focus being too much on risks and ensuring safety, thereby stifling innovation. Applying SbD could be a way to establish iterative, appropriate risk management techniques and in that sense, also place focus on the potential benefits. This way, ensuring safe development and implementation of innovations is highly regarded, but the pros and cons can become more balanced. Additionally, SbD puts more emphasis on learning what potential risks entail, thereby raising awareness, which is always helpful in arriving at safer, more responsible innovations. iGEM certainly creates a suitable environment to do so.

Concluding remarks

One of the aims of this paper was to contribute to the SbD knowledge base by supplying concrete examples of how this approach is operationalised in practice, and to illustrate how we have embedded ‘designing for safety’ in education. Thereby, we hope to have inspired and supplied tools for researchers and lecturers working in the field of synthetic biology to implement the SbD approach in their research and/or education.

A crucial aspect of ‘designing for safety’ is awareness. We hope that emphasis being placed on this notion and embedding both VSD and SbD in education helps to increase students being aware of such and to make design choices accordingly. In addition, students taking part in iGEM are also incentivised to pay great attention to safety aspects through the iGEM Foundation itself. As they regard safety and security highly, they award one project with the ‘Best Safety & Security’ every respective year. Also, to win the ‘Grand Prize’, projects should be ‘overall excellent’ and need to score high on all aspects, in addition to technical achievements.

Besides tools that specifically aim to assist iGEM teams (e.g. the iGEMers guide to the future as part of the SYNERGENE project (Rathenau Instituut 2015; Stemerding 2015)), many more approaches and tools have been developed to help researchers in general to reflect on their work in bio-engineering and to arrive at responsible designs. For instance, applying techno-moral scenarios for researchers to explore moral controverses that can emerge as a result of emerging technologies (Swierstra et al. 2009), the 'Wheel of Action, Interaction and Reflection' (WAIR) tool to help researchers anticipate potential environmental, social and safety impacts of their technology (Athena Instituut - VU Amsterdam, n.d.), or 'Biofiction' – a film festival to initiate debate about the evolution of synthetic biology (Schmidt, Meyer and Cserer 2015).

This paper focused mostly on biosafety measures through SbD, but iGEM projects also considered biosecurity aspects to a great extent, in particular the risk of misuse. As imagining different usage can be hard, all TU Delft iGEM teams contact the Biosecurity Office, part of the Dutch National Institute for Public Health and the Environment (in Dutch: RIVM). In 2021, they have developed a tool for dual-use research of concern evaluation, the 'Dual-Use Quickscan' (Biosecurity Office, n.d.; Vennis et al. 2021). This web-based tool consists of a questionnaire that enables identification of potential issues on dual-use of the product, but also again uses this data to contribute to the general awareness of dual-use.

Additional notes

PHOCUS (2020) has won the iGEM special awards for 'Best Safety & Security' and 'Best Integrated Human Practices', besides receiving additional nominations and awards. For more information on the project, please see: https://2020.igem.org/Team:TUDelft.

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Note

1. Although iGEM does not allow projects to be brought outside the contained environment of the laboratory, students must think about a possible, eventual application of their project in real-life.

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Appendices

Appendix A: PHOCUS

Table A1. Identified stakeholders and derived values. From: iGEM 2020 'PHOCUS' VSD Assignment – ELSIB course. *Values were retrieved from organisation's respective website. **Values were interpreted from other sources (e.g. media) or from empirical findings (i.e. interviews).

Stakeholder	*Values*
Ministry of Agriculture, Livestock, Fisheries and Irrigation of Kenya*	Professionalism Integrity Efficiency and Responsiveness Partnerships Gender Equity
Food and Agriculture Organisation (FAO)**	Health Equality Accessibility Food Safety Food Security Environmental Safety Sustainability Innovation
Desert Locust Control Organisations East Africa**	Cooperation Food Security Innovation
Kenyan farmers and herdsmen**	Family Health Economic Benefit Status Food Security Personal Autonomy
Sumitomo Chemical*	Integrity Passion Innovation Collaboration Responsibility Economic Benefit

(*Continued*)

Table A1. Continued.

Stakeholder	Values
iGEM*	Integrity Good Sportsmanship Respect Honesty Celebration Cooperation Effort Excellence

Table A2. Translation of selected values into norms and design requirements. Only values that can result in tangible design requirements are included in this Table. From: iGEM 2020 'PHOCUS' VSD Assignment – ELSIB course.

Value	Norm(s)	Design Requirement(s)
Health	No effects on physical or mental health	• Bacteriophages as genetic carriers • No delivery of bacteriophages under acidic conditions • Non-toxic, non-pathogenic host microorganism that is not present in humans • Produced toxin non-pathogenic to humans and degradable in human digestive tract
Accessibility	Access to the product at all times Access to knowledge about the product	• Robust distribution network • Local production • Affordable • Simple and easy to use • Provide sufficient knowledge to end used for an educated decision
Food Safety	Low or limited presence of hazardous compounds	• No toxin production outside the locust • Toxin should be non-toxic to humans and livestock, and degrade when exposed to the outside environment
Environmental Safety	Production is not harmful for the environment Usage is not harmful for the environment	• Production in cell-factories • Toxins very specific to locusts • Use virulent bacteriophages • Insertion of a kill switch driven by light • Physical barrier between the environment and the bacteriophages
Sustainability	No irreversible effect on the environment	• Production cell-factories • Agricultural waste as feedstock • Storage system based on sunlight • Local Production of bacteriophages • Product unstable outside locusts
Integrity	Business interest should be in harmony with public interest Adherence to your values no matter the circumstances No underlying agenda	• Actions taken to achieve the goals should always be in accordance with the values stated, no matter the contact or situation faced • Should not be affected by political instability or misconduct • Decisions made in the design process should be transparent and clearly communicated
Efficiency and Responsiveness	The product should be producible and deployable on short notice Measures against locusts should be highly efficient	• Easily scalable cell-factories for production • Minimise required amount of toxin • High level of toxin production in a short amount of time • Use of anchoring proteins to increase the specificity
Collaboration	Collaborate with stakeholders Earn trust of stakeholders	• Approval for local, regional and cross-border use • Adjusted to needs of different stakeholders • Transparent design choices and knowledge sharing
Food Security	Upsurge of plagues should be controlled	• Highly toxic and specific toxin

(*Continued*)

Table A2. Continued.

Value	*Norm(s)*	*Design Requirement(s)*
	Adequate resources for nutritious food should be available	• Tackle locusts before they are swarming and/or kill them efficiently • No negative effect on the growth of the crops • Toxin should not reduce the nutritional value of the food
Economic Benefit	Users should benefit economically Producers should benefit economically	• Cheaper than current products • Large yield of toxic per quantity of phage • Rapid spread of the phage amongst locusts • Fast replicating phage • Profitable production and sale
Personal Autonomy	Being able to make own decisions Users willingly use the products	• Sufficient information about the product's availability • Deciding not to use the product does not result in punishment in what so form • No higher power or legislation influences potential users
Responsibility	Cannot be used in a harmful way Beneficial to society	• Highly specific bacteriophage which cannot be tuned and used for other purposes • Regularly re-evaluate the design • Involve different stakeholders in design process and use their input to improve design • Inform the public about the product

Appendix B – AptaVita

Table B1. Identified stakeholders and derived values. From: iGEM 2020 'AptaVita' VSD Assignment – ELSIB course.

Stakeholder	*Values*
World Health Organisation[1]	Health Equality Inclusivity Honesty Trustworthiness Sustainability Accessibility Safety Quality[3]
Center for Disease Control and Prevention[1]	Health Equality Prevention Efficiency Quality[3] Safety
Food and Agriculture Organisation[1]	Food Safety Health Sustainability Equality
Government of Uganda[2]	Health Equality Food Safety Education Efficiency Accountability
Local Ugandan Communities[2]	Trustworthiness Acceptability Accessibility Health
Point-of-care clinics[2]	Health Safety

(*Continued*)

Table B1. Continued.

Stakeholder	*Values*
Astel Diagnostics[1]	Accessibility Trustworthiness Quality[3] Health
iGEM Foundation[1]	Accessibility Trustworthiness Integrity Excellence Respect Effort Honesty Cooperation

Figure 5

1. The values are retrieved from their respective websites and reports.
2. The values are derived from other sources, i.e. interviews.
3. Quality is referred to as accuracy and reliability.

Table B2. Translation of selected values into norms and design requirements. Only values that can result in tangible design requirements are included in this Table. From: iGEM 2020 'PHOCUS' VSD Assignment – ELSIB course.

Value	*Norm(s)*	*Design Requirement(s)*
Health	Avoid any negative impact on physical, mental and social well-being of people	The value health stands at the core of all other values. Therefore, thedesign requirements that are elaborated on in the following sections are also the design requirementsfor health as a value.
Quality (Accuracy & Reliability)	Measurements should reflect the true valueMeasurements should be consistent	• Control with a ligand at known concentration • Mobile readout • Use of blood • Develop sensible and selective aptamers • Use of a robust cell free system
Efficiency	Avoid wasting materials, efforts, money and time while achieving the desired result	• Ready-to-use RDT• Use of a fast-expression cell free system• Inexpensive materials• Small reaction volumes
Safety	Production, use and disposal of the RDT should not be harmful to the environmentProduction, use and disposal of the RDT should not harmful to the user	• Non-GMO, use of cell-free system • Provide use and disposal instructions • Use of non-toxic components
Equality & Inclusivity	Everyone should have equal access to RDTProduction and use of RDT should not lead to discrimination on any basis	• Frugal innovation • Manual should be in native language • Include local community in production/ value chain
Trustworthiness & Acceptability	The device should inspire confidence and reliance in the userThe devise should be readily approved by the user, should be willing to use the device	• Use blood as sample • Reliable producer • Use of cell-free system • Use of urine or saliva as sample
Accessibility	RDT should be available at the point of care (physical)RDT should be affordable (economic)RDT should be understandable (information)	• Freeze-dried system stable at ambient temperatures • Use of cheap reactives and small reaction volumes • Include a user manual
Sustainability	Reduce ecological footprintReduce social dependency	• Freeze-dried system stable at ambient temperatures • Use recycled/biodegradable packaging materials • Small reaction volume • Local/regional production