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Artificial Cornea (Keratoprosthesis) – A Nanotechnologically Modified Biomaterial To Restore Eyesight To *Ultima Ratio* Patients

Loss of eyesight, may it be caused by accidents or diseases, is associated with a substantial decrease in the quality of life. There is little doubt that restoring functional vision does not justify each and every means of disposal to a specialist. In this framework, the ethical ramifications associated with ameliorating ophthalmological deficiencies are remaining to be subject to considerable debate. A few of them are: What constitutes 'sufficient data obtained from assays in model systems' to justify testing visual prosthetics and/or procedures in clinical trials. Does the expected outcome in the sense of improvements to existing procedures and remedies justify risking the well-being of healthy volunteers?

The aim of this article is to present the successful creation and implantation of an artificial cornea on the one hand and highlight ethical questions the authors had to face in the progress of their project.

When the Window to the World is Broken

In its essence, one can equalize, albeit on a conceptual level, the human cornea to the window to our world, or even the front lens of a photographic device. The adult cornea is thinner than one fiftieth of an inch and can be divided into five compartments: the surface epithelium, which is in contact with the tear film, directly underneath Bowman's membrane, followed by stroma, Descement's membrane and the endothelium (DelMonte and Kim 2011).

The anatomy of the cornea provides vulnerabilities to infections with the gram-negative bacterium *Chlamydia trachomatis*, which, in its terminal stages, leads to corneal opacification and de-facto blindness, considered to be a preventable cause of blindness (Dean et al. 2008; Rajak et al. 2012; Whitcher et al. 2001). In such cases, see Tan et al. 2012 for a review on other indications, corneal transplantations are recommended, although the demand for transplantable corneas is greater than the supply (Golchet et al. 2000).

Early reports of the development and successful clinical use of artificial corneas are reviewed by the French ophthalmologist de Quengsy (De Quengsy 1789). Re-examination of this record revealed that de Quengsy suggested a corneal replacement with a porous skirt to aid correct posi-

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tioning and functionality (Chirila and Hicks 1999; DeVoe 1977; Rintelen 1974). This concept of an artificial matrix to embed the implant is being employed today and, naturally, subject to refinement, see (Eguchi et al. 2004; Hicks et al. 2000; Legeais and Renard 1998) as references to in-depth discussions of the results of respective clinical trials.

One of the underlying principles of the generation of a biocompatible corneal implant is the appropriate functionalization of surfaces. For one, the embedding tissue should readily accept the device and serve as permanent anchor of the implant in the host tissue. Additional support for the implant may come from autologous material, where immunological tolerance may be favorable, even though altered properties of the microenvironment, perhaps tilted by micro-infections or other contributing factors, may switch the balance of stromal signals to favor apoptosis (Izumi et al. 2006; Yanai et al. 2002; Mohan et al. 2000), observed as clinical manifestation of tissue 'melting' (Hicks et al. 2000).

Examples of insufficient biocompatibility seen in clinical trials using Biokpro II and the Boston keratoprothesis type 1 include encapsulations, probably caused by inflammations (Legeais and Renard 1998; Rudnisky et al. 2012). This also means that the chemical and physical properties of the polymer substrate, applicable coatings and general structure(s) of surfaces need to be designed according to the desired function of the implant and insure ease of handling, an apparent problem associated with the AlphaCor (Eguchi et al. 2004).

While all of the above-discussed implants do not require intra-capsular lens extraction but appear to require refinement, an alternative approach, the osteo-odonto keratoprothesis (Casey 1966), this device at present-day refinement levels may be an additional tool in restoring limited field of vision to ultima ratio patients, as reviewed by (Rudnisky et al. 2012; Tay et al. 2007). Still, it appears to be that corneal replacements, based on synthetic polymers, are accompanied by side-effects that may very well render these devices as truly ultima-ratio and perhaps short-term remedies.

Alternative approaches to build corneal materials that are suitable for transplantation, may involve bioengineering routes, fuelled by the enthusiasm generated by a pioneering report of the construction if functional corneal equivalents from immortalized cell lines, derived from the individual compartments of human corneas (Griffith et al. 1999). Attempts to build on these observations by using re-programmed cells on scaffolds to produce corneal material cannot, however, address the concern that such cells may favor tumor growth, if not go down a malignant route themselves (Espandar et al. 2012; Yu et al. 2008). This line of reasoning, however, should not be construed as reason for a dampened enthusiasm, when it comes to assessing the validity of studies using such materials for proof-of-principle studies and basic research to advance the bioengineering field.

The Making of a New Window to the World

The above-referenced evidence strongly supports the formulation of basic requirements for the corneal replacement: compatibility with the host tissue, pliability to mimic natural anatomic features of the cornea, and translucency to permit image projection.

As partially described elsewhere (Storsberg 2012; Storsberg et al. 2011), this implant is supported by a hydrophobic base material with differentially functionalized surfaces. In essence three functionalities are desired, aside from complete biocompatibility of the base plastic and all subsequent modifications: One, the haptic of the implant needs to safeguard proper anchorage within the host tissue. Two, the optic posterior needs to be permissive to the projection of images, meaning that

cell growth, adhesion, motility and deposition of extracellular matrix are inhibited, individually and collectively. The optic anterior needs to allow formation of a functional tear film and proper movement of the eye lid (Figure 1).

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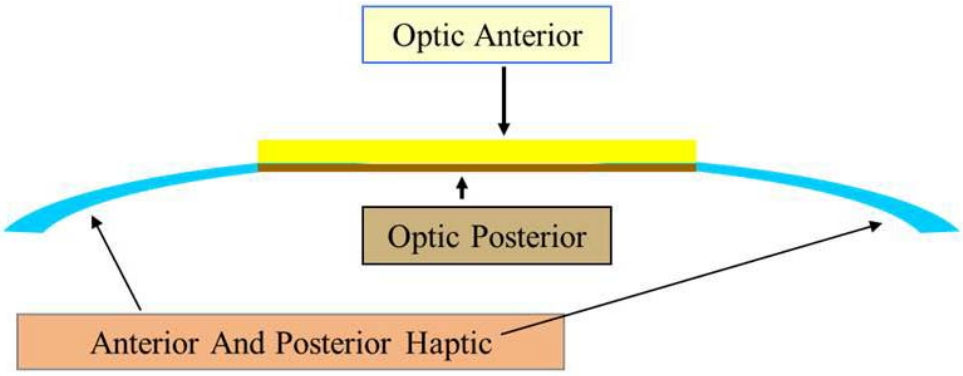

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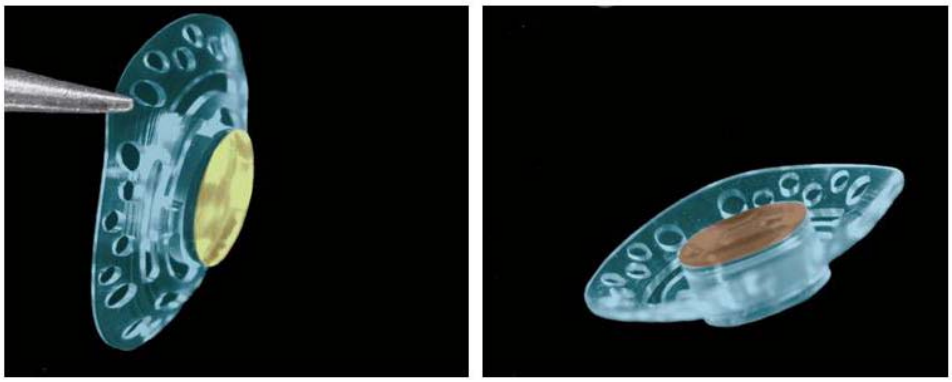

Fig. 1: Desirable surface properties of the new keratoprosthesis.

(a) Schematic illustration of differentially functionalized surfaces.
Shown are the haptic anterior and posterior (in blue) where tissue in-growth is promoted to firmly anchor the implant into the host tissue. Optic anterior and posterior are indicated with yellow and brown boxes, respectively. Note that the formation of the tear film and lid movement occurs proximal to the optic anterior, necessitating appropriate functionalization of these surfaces.

(b) Artificially colored photograph of a new keratoprosthesis.
Anchorage of the device in the host tissue is achieved via special surface modification of the haptic (shown here in blue). Specifically, growth and attachment of cells as well as deposition of extracellular matrix is promoted on these surfaces. In stark contrast, the surfaces of optic anterior and posterior (colored yellow and brown, respectively) are inimical to adhesion of cells and deposition of extracellular matrix, thus, rendering the optic permissible to the transmission of light and images. © Fraunhofer-IAP

In execution, a hydrophobic base material was selected that retains its transparency was selected for the generation of this next-generation implant (Storsberg 2012; Storsberg et al. 2011). To aid subsequent modifications, atmospheric plasma was used to activate the surface (Figure 2). Briefly, the material was brought in contact with the plasma for no longer than five minutes per square centimeter surface area. To allow for different functionalization of the optic anterior, this area was covered with a metal plate during the activation of the haptic anterior (Figure 2). Note that activation of the haptic posterior involved covering the optic posterior whilst exposing the surface to the plasma beam (not shown).

Successful activation of the surface was verified by assaying for changed contact angles of physiological buffer, similarly to the references provided in (Lee and Yang 2012). Due to the hydrophobic nature of the polymer used, plasma activation was expected to temporarily alter surface properties such that spreading of water-based formulations of buffers would increase. As expected, activation of surfaces with the atmospheric plasma yielded quasi-hydrophilic surfaces, as demonstrated by decreased contact angles before and after treatment of surfaces with atmospheric plasma (data not shown).

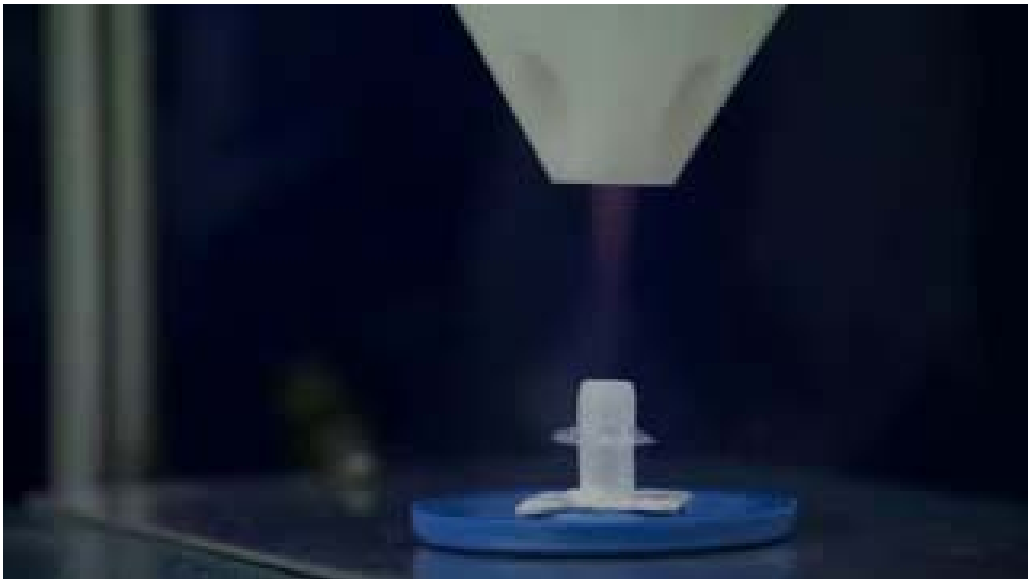

Fig. 2: Activation of the haptic surfaces using atmospheric pressure plasma.

Shown is a representative image of an activation of the haptic surface using atmospheric plasma. Note that the optic anterior and posterior surfaces are covered (see Storsberg 2012; Storsberg et al. 2011 for details). © Fraunhofer

After successful activation of the surface, polyelectrolytes (Chitosan and Heparin) were layered onto the haptic using the formation of multiple layers of polyelectrolytes, approximately 7nm in thickness (Wu et al. 2012; Ladam et al. 2001; Decher 1997). Briefly, sequential addition of the polyelectrolyte solution in water, followed by removal of excess material by washing in water yielded a 7nm thick polyelectrolyte layer, suitable for the adsorption of peptides for proper adhesion (see Singhvi et al. 1994; Chen et al. 1998 as references regarding geometry requirements for adhesion and Barkan et al. 2010; Ivaska and Heino 2010 for further reading on the role of the extracellular matrix on the adhesion and growth of cells). Successful surface modification was tested in a tissue culture setting using primary porcine lens epithelial cells of the first passage. After 8 day, phase-contrast microscopy of live cells was performed. As shown in Figure 3, differential modification of surfaces of one and the same base material was successful and no cytotoxicity was detected.

Based on these observations, this device was then tested for biocompatibility and functionality in rabbit eyes in accordance with all applicable laws, regulations and ethics protocols. Rabbits were anesthetized and the host cornea of one eye was replaced with an intra-stromal and an epicorneal keratoprosthesis (KP), respectively (see Busin 2003 and Choyce 1965 for further reading on surgical methods). The implants were removed four weeks later and the animals were sacrificed. Exemplary, the result for one epicorneal KP is shown in Figure 4. The device caused no complication

over the life time of the implant, suggesting reasonable biocompatibility and functionality in a model organism.

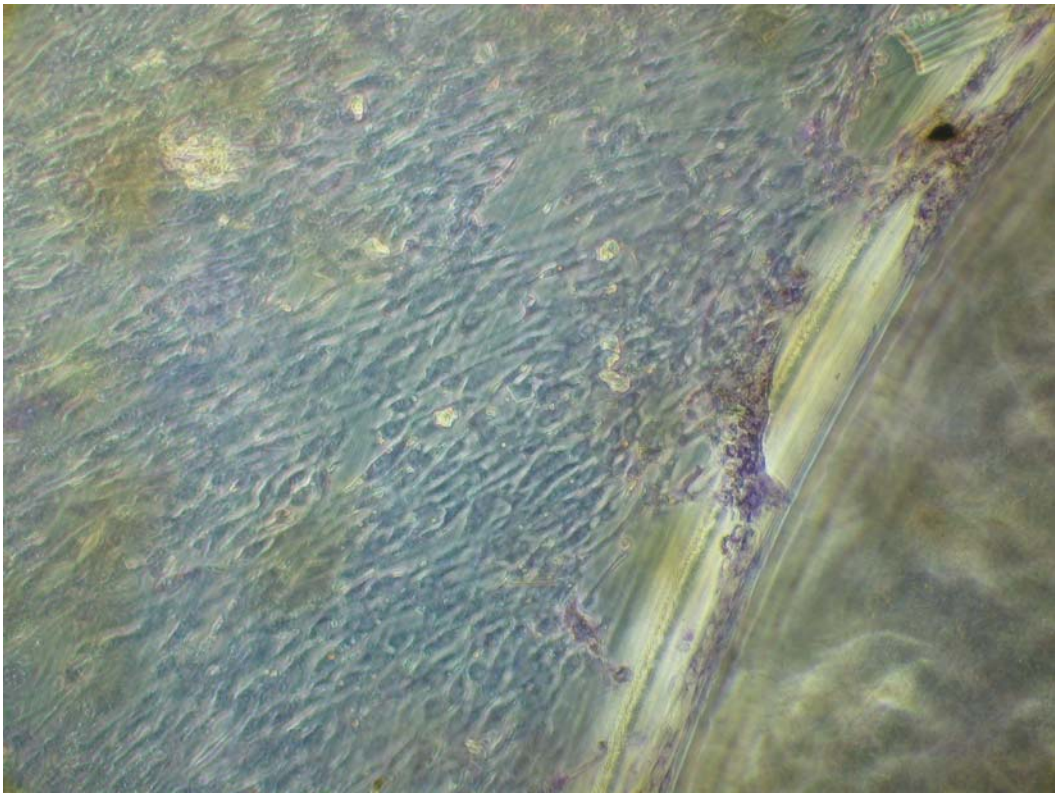

Fig. 3: Representative phase-contrast photography of primary, porcine lens epithelial cells grown on a differentially surface-modified cornea replacement.

Shown here is a phase-contrast of primary porcine lens epithelial cells of the first passage grown on the material for 8 days. Robust growth of cell clusters can be seen on the haptic. In comparison, significantly smaller clusters of cells with the appearance of blebbed cells, indicative of late-stage apoptosis (Kerr et al. 1972), are seen on the optic anterior (and data not shown). Thus, it is concluded that neither the material nor any subsequent handling impairs cell growth on the haptic. Note that growth of cells occurs right to the edge of haptic and posterior optic. As seen here, no crawling of cells could be observed, which is in accord with the geometry of adhesion (see text for details). This image was previously published in Storsberg et al. 2011.

Successful implantation of the MIRO KP into an ultima ratio patient

Developing a new device and testing it in patients who have a substantial interest in receiving therapy presents an ethical dilemma that is being discussed in the literature (see Dudzinski et al. 2010 and Daugherty 1999 as a guide for further reading). Trust between the patient and the caring physician is at the center of a relationship, ideally preceding to and lasting after the clinical trial has passed on. This trust is part of a larger network of elements feeding into the decision-making process, one of them being the perceived or measurable reputation of the research or the hosting institution where the research was or is being performed (see Ippoliti and Falavigna 2012 for a good introduction into this sub-field of medical ethics).

Trust between patient and physician, manifested perhaps in a full disclosure of potential hazards and risks associated with this experimental therapy and a patient's full comprehension of the great-

er implications, is not truly sufficient to address the inherent issue of ethics in medical research. For instance, Dudzinski et al. (2010) review the dilemma of disclosure of adverse effects that may or may not 'cross the threshold' of 1 out of 10,000 patients being 'potentially affected' – aside of differences in the interpretation of, say, 'crossing a threshold' and 'potentially affected' in the fields of biomedical research and jurisprudence. Nor is the concept of fully informed and cohort-tailored consent, as defined by Daugherty (1999), formally required to fulfill the requirements of truly ethical clinical research.

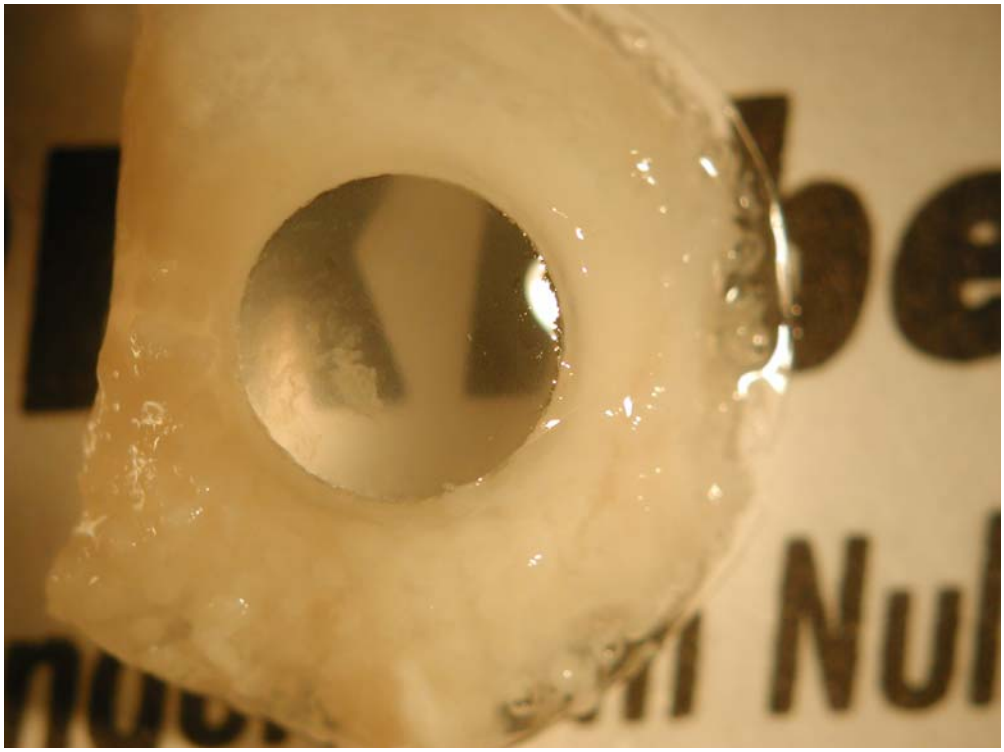

Fig. 4: Photograph of an epicorneal keratoprosthesis with differential surface modification after 4 weeks of implantation into a rabbit eye.

Surface modification occurred precisely as described above and γ-sterilized. Note that the skirt (haptic) is overgrown with tissue whereas the optic (anterior and posterior) is permissive to transmission of light, adding further credentials to earlier observations that surface modification on one and the same base material could be employed to mimic corneal functionality with an synthetic polymer-based implant. All *in vivo* tests were performed following the ethical guidelines and were approved by the ethics committee of the Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany. This image was previously published in Storsberg et al. 2011.

Another area of discussion is the question whether clinical research can be successful if there is no possibility to test new products (e.g. drugs, implants or diagnostic devices) in humans. Imagine that scientists have developed a new drug that, from existing evidence, may be seen as being effective but nobody wants to or can be convinced to test it in a clinical trail. However, in order to expand our knowledge, at some point somebody must take this new drug. This is not a selfish wish for scientists but needs to be done for the greater good of patients, currently suffering from a disease and interested in amelioration of their symptoms, if not being cured of this malady. This brings us to a point where we, clinical researchers and physicians alike, argue in support of the case that the drug must be tested in a controlled clinical study by someone in order to prevent serious or even fatal side effects, if usage of the drug or employment of the treatment approach provides indeed a significant advantage to the overarching goal of improving a patient's condition.

(a)

(b)

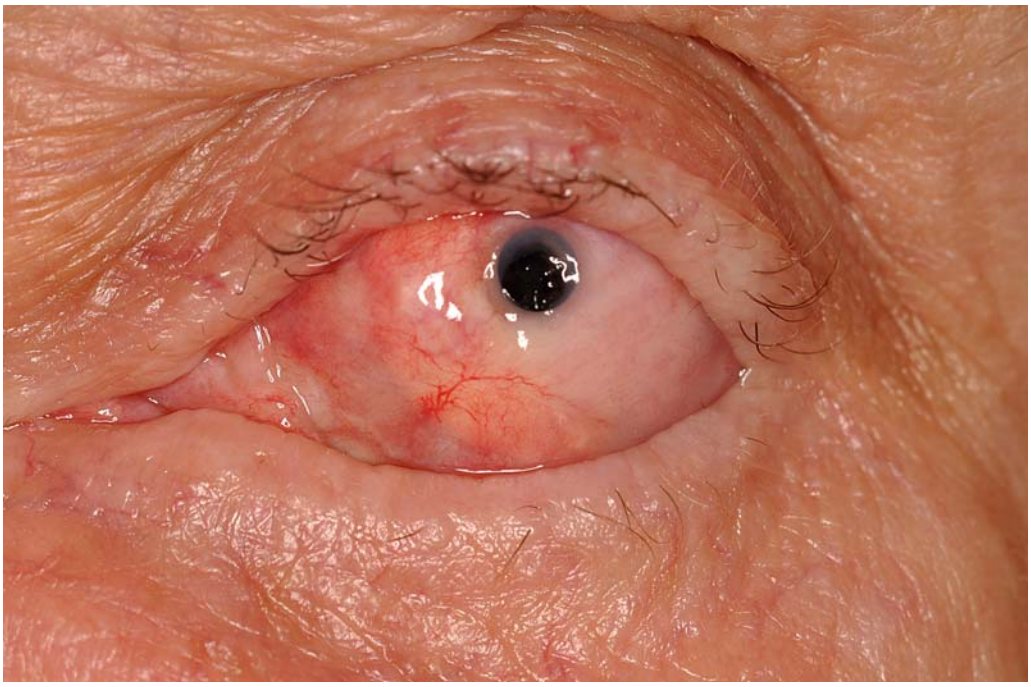

Fig. 5: Successful implantation of the keratoprosthesis into an ultima ratio patient.

(a) Keraprosthesis for implantation into an ultima ratio patient.
Shown here is the final and dried product with all surfaces properly modified. © Fraunhofer-IAP/Okulla

(b) Implantation of the keratoprothesis into an ultima ratio patient.
The photograph of the patient's eye with the implant is taken one year post surgical intervention. This image was previously published in Storsberg et al. 2011.

Addressing this area of concern, Emanuel et al. 2000 formulated a set of universal requirements to guide individual adaptations in the context of specific projects to be undertaken, from the conceptual level of planning to the execution of a study protocol:

1. Weigh the benefits gained from the execution of the study against the social and economic costs of this project, e.g. independent scholarly review and fair selection and treatment of subjects. The benefits must outweigh the associated costs.
2. Participant's autonomy needs to be respected by granting informed consent by disclosing benefits, risks and alternatives.
3. Patients must be free to terminate study participation at any time.

The *logical* consequence of these arguments, especially the call for informed consent, is that it is ethically questionable to withhold scholarly information from the public via subscription walls. As an alternative, Krumholz 2012 provides strong arguments in favor of the dissemination of published evidence free of charge to the public, also known as Open Access. It has to be noted, however, that connectivity to the Internet remains necessary to access this information (see Suber 2012 and references therein for further reading on Open Access).

The *ethical* question of whether and how a clinical trial should be conducted cannot and should not be answered in the context of this article. It is a question of social and philosophical aspects. The different dimensions cannot be dealt with all facets within the narrow scope of this paper. Here, we only intended to stimulate the discussion in order to re-considerate and re-evaluate existing opinions and views.

The *social* aspects are based on the structure of the society in which it the particular individuals are living their life. Arrangements for living together can be determined for the society only if moral and ethical values, held by people in this particular society, are in perfect, or at least reasonable, alignment with each other. As an active member of this society, each individual must first form an opinion on the question as to how the social life should be regulated. Then, by utilization of democratic means of reaching a decision, it should be decided on a way that is considered to be the best way ahead for the majority of society. This, ideally, should be codified in form of laws and regulations as a means to preserve and advance the universal and greater good.

The *philosophical* and *moral* approach, underlying these discussions and decision-making processes, as well as their implementation and, if needed, enforcement, would, at least in the opinions of the authors of this paper, help the people in a society to discus and clarify the issues at a higher level of consciousness. For example, the *categorical imperatives* formulated by Immanuel Kant may be seen as good point of reference: "Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to end on, but always at the same time as at end." (Kant 1785). Without further deepening this issue, we only want to mention some of the issues society and the scientists may have to deal with. It is, however, important to know whether everything possible should and could be done. The consequences of the answers to the areas of concern, outlined above, must be known, or at least taken into reasonable account and consideration, for the effects on individuals and on society at large. The patient, and the physician alike, must be able to properly assess the extent of their actions.

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Space considerations forced us to select citations and limit the scope of this review. Our selection of citations does not imply that we believe the papers cited are superior to the references available for citation. We, therefore, wholeheartedly apologize to all colleagues whose significant contributions are not cited and discussed in this paper.

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