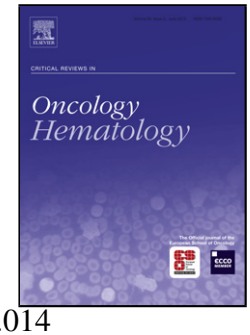

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PII: S1040-8428(17)30442-0
DOI: https://doi.org/10.1016/j.critrevonc.2017.12.014
Reference: ONCH 2478

To appear in: *Critical Reviews in Oncology/Hematology*

Received date: 25-9-2017
Revised date: 27-11-2017
Accepted date: 19-12-2017

Please cite this article as: Carrieri D, Peccatori FA, Boniolo G.The ethical plausibility of the 'Right To Try' laws.*Critical Reviews in Oncology and Hematology* https://doi.org/10.1016/j.critrevonc.2017.12.014

The ethical plausibility of the 'Right To Try' laws.

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Abstract

'Right To Try' (RTT) laws originated in the USA to allow terminally ill patients to request access to early stage experimental medical products directly from the producer, removing the oversight and approval of the Food and Drug Administration. These laws have received significant media attention and almost equally unanimous criticism by the bioethics, clinical and scientific communities. They touch indeed on complex issues such as the conflict between individual and public interest, and the public understanding of medical research and its regulation. The increased awareness around RTT laws means that healthcare providers directly involved in the management of patients with life-threatening conditions such as cancer, infective, or neurologic conditions will deal more frequently with patients' requests of access to experimental medical products. This paper aims to assess the ethical plausibility of the RTT laws, and to suggest some possible ethical tools and considerations to address the main issues they touch.

Keywords

Right to try laws, terminally ill patients, clinical ethics, clinical trials ethics, ethical counselling, trusted consent

1. Introduction

The Right to Try (RTT) laws originated in USA in 2014 at the Goldwater Institute, a conservative libertarian public policy think-tank in Phoenix, Arizona (1). They allow terminally ill patients (patients in an advanced stage of a disease with an unfavorable prognosis and no known cure) to request access to early stage experimental (with as-yet-unknown efficacy and adverse effects) medical products (drugs, treatments, biologics, and other medical devices), directly from the producer, removing the oversight and approval of the Food and Drug Administration (FDA). Although based on the Goldwater Institute's blueprint, they vary between different states. The main RTT laws requirements (2) are:

- The patient has a diagnosis of a terminal disease (which in some states includes permanent coma) and no other treatment options are available.
- The experimental product has passed Phase 1 safety testing and is at least in early Phase 2 safety and efficacy testing.
- The patient's healthcare provider (HCP) recommends the experimental medical product.
- The patient, or a designated guardian, has given informed consent to take this product

The HCPs are expected to give patients a description of the best and worst possible outcomes using an experimental treatment. However, the RTT laws absolve HCPs and producers (the pharmaceutical or biomedical company or manufacturer developing the product) from legal liability from any harm the experimental medical product can cause to patients. RTT laws are underpinned by the presumption of patients' capacity to weigh

the risk and benefits and make informed medical decisions based on the information provided by their HCPs, and on their own values and desired outcomes.

The first RTT law was passed in Colorado in 2014, and currently (November 2017) there are RTT laws in place in 38 states[4]. RTT bills have been introduced by both Republicans and Democrats and they have passed with unanimous support. These laws have proved very popular and have received significant media attention. In contrast, they have also received almost equally unanimous criticism by experts in the bioethics, law, clinical and scientific communities (3).

1.1. Background: FDA Expanded Access

Before entering the heart of the controversies, some background information is needed to understand the context in which RTT laws have emerged. When available treatments are ineffective, some patients with serious or terminal illnesses may wish to try experimental medical products, in the hope of receiving therapeutic benefit. The standard way to access such experimental products is by participating in a randomised control trial (RCT). As known, new medical products are not available to the public until they have been tested in Phase 3 of clinical trials; shown evidence of safety and efficacy; and gained approval from the FDA. This testing and approval process can take up to 10-15 years. RCTs also require specific eligibility criteria that may preclude certain patients from participation, and these criteria often exclude terminally ill patients because they are more likely to develop adverse outcomes, risking both their lives and to jeopardise the RCT. Currently RCT access is also limited by patient geographical location, with rural areas particularly penalised. Therefore, terminally ill patients who do not qualify for or do not have access to a RCT may die waiting for a medical product to be approved and accessible. Moreover, terminally ill patients who can access RCTs, may not wish to risk to take the 50% chance of being assigned to a control group (who often receives a placebo or an already approved treatment, which would be ineffective for such patients) and therefore not obtain timely access to the experimental medical product they seek.

These are among the main factors that have led some patients to seek experimental medical products on their own, also illegally from black or 'grey' markets (from other patients who sell their pills or share the ones they got in trials) (4). Since the 1970s, the

[4] http://righttotry.org/in-your-state/

American patients have also legally pressured the FDA to expand access to experimental medical products. Under current FDA regulations, patients with serious or life-threatening conditions can apply for Expanded Access (EA) to experimental treatments outside of a clinical trial and before the experimental medical product has been approved by the FDA[5]. This requires approval by both the FDA and by an independent Institutional Review Board (IRB) at the hospital or institution where the treatment will be administered. The objective of the EA programme is to balance speed and safety of access for the requesting patient, without interfering with the conduct or completion of the RCT (5). Some important measures help to achieve this objective:

- The IRB acts as an independent third party whose tasks include reviewing research protocols; assessing the risks and benefits to safeguard patients; review consent forms, in particular the language and terminology used, to help ensuring that consent is informed and voluntary.
- Before the FDA considers a request for EA the producer must agree to provide access to the product outside a RCT. The FDA can act as mediator between the patient and the producer, but has no authority to override a producer's decision to not provide access.
- Once access is given, the HCPs have to report follow-up clinical data about the patient to the FDA (6).

EA is normally granted for experimental medical products in Phase 2 or 3 in circumstances where there are no alternative therapies and the patients are ineligible or unable to participate in a RCT. It is important to highlight that EA also allows patients with immediate life-threatening conditions to apply for access to experimental medical products that have passed Phase 1 of RCT (7) – the same threshold of the RTT laws. However, unlike the RTT laws, the FDA always requires data suggesting the medical product is safe enough to give to patients.

In recent years, the FDA has approved more than 99% of EA requests it received and has speeded up the approval process (8). The current FDA EA form normally takes 45 minutes for HCPs to complete, and the FDA can answer emergency requests for EA in 24 hours (8, 9).

[5] We are briefly recalling only the American case, where the RTT laws have been implemented. The regulation, and terminology, for what is here called 'expanded access' varies from country to country.

To conclude this bird's-eye view background, it is also important to point out that FDA EA and RTT laws are only a part of a broader set of diverse efforts to make medical products available before the completion of RCT (still considered the gold standard to assess the safety and efficacy of medical products), and/or to design different, faster methods. For example, surrogate endpoints, biomarkers or intermediate end points are increasingly used to substitute RCT and predict patient relevant outcomes (10). In 2014, the same year of the first RTT laws, in the context of the Ebola outbreak in West Africa, the World Health Organization declared that it is ethical to offer experimental interventions, provided that certain conditions are met (11). The Wellcome Trust (UK) has drafted guidelines to fast-track trials in humanitarian emergencies (12). The USA 21st Century Cures Act (21CAA) developed in 2016 encourages the FDA to consider new evidentiary standards in the development and approval of new medical products, including data from Electronic Health Records (EHR).

1.2 Relevance of discussing RTT laws

Although RTT laws have emerged in the USA, the difficult issues they touch upon, and the complex area of end of life care in which they are situated, are relevant to other countries (13). Such issues include: the balance of therapeutic beneficence between medical research centred on the public and clinical practice centred on the individual patient; the potential conflict between individual medical autonomy and the interest of public health and medical research; the public understanding of (and trust in) the process and regulation of medical research. These issues are not only of interest to clinical, medical scientists and other experts from different disciplines such as clinical lawyers, health regulators, social scientists, and bioethicists. The increased awareness around RTT laws – also ignited by a recent popular Hollywood movie 'Dallas Buyers' Club', and by other stories of individuals who have attempted to obtain experimental treatments – means that it is likely that HCPs will deal more frequently with patients' requests for access to experimental medical products. This will particularly be the case for HCPs directly involved in the management of patients with life-threatening conditions such as cancer, infective, or neurological conditions.

1.3 Aims and outline of the paper

We aim to provide a set of ethical tools and considerations that may help to address the main issues touched by the RTT laws and their critics.

In order to illustrate the key controversies of the RTT debate, we begin by reviewing the main arguments in favour (section 3) and against (section 4) RTT laws. RTT advocates claim that the laws support individual autonomy by removing unnecessary and time consuming 'regulatory walls' between terminally ill patients and the experimental products which may have some therapeutic benefit. Critics have expressed concerns about the real efficacy of these laws; the nature of the 'right' they confer to patients, and how they may contribute to health inequalities. They are also concerned about the negative consequences that unregulated access to experimental medical products may have for the patient requesting access, end of life care, the sustainability of medical research and clinical trials, and for public health. In line with some literature (14), we acknowledge that RTT laws are situated within an important debate about how to improve terminally ill patients' quality of life and decisions, but we argue that they do not provide an effective means to achieve this objective.
The issues touched by the RTT debate are very complex and blend clinical, research, and social challenges. To tackle this complexity – and to address most of the concerns of RTT advocates and its critics – we outline in section 5, a multi-pronged approach. First, we suggest two complementary ethical tools to improve end of life decision making (promoting autonomy and quality of life for terminally ill patients, also beyond the problem of access to experimental treatments). These are models of consent based on trust, and an ethical counselling framework aimed at both patients and HCPs. We are also cognisant of the structural and social complexity of the processes and regulation of medical research, which is intensified by a 'communication gap' between experts and the public. Therefore, we suggest stakeholder engagement to inform the design and regulation of clinical research, considering the perspectives of the stakeholders; and more, more balanced, communication and education campaigns to foster constructive stakeholder engagement. Finally, we press that stakeholder engagement and any participatory endeavours should promote changes in RTT, or develop other programmes, that do not increase economic unfairness and inequality, unlike the current version of RTT laws.

We searched the literature on RTT in three databases: PubMed, Web of Science and Google Scholar. We looked for publications with the key term 'right to try' in the title and/or abstract. Inclusion criteria for articles were English-language commentaries, reviews, and papers. We also searched through relevant journals separately to ensure we

had not omitted any relevant literature, and we found additional literature through citation tracking and snowballing. To complement our search, we explored some relevant grey literature including: blogs, online articles, reports, and university dissertations.

The vast majority of the academic literature identified discuss RTT issues focusing on the USA, with some exceptions of papers which adopt a global public health perspective (15), analyse both UK and USA (13), and USA and Europe (16). Most articles address RTT from clinical practice (mostly oncology), medical research, legal and ethical angles, and one from psychiatry (17).

Most papers tend to be either strongly critical of the RTT laws' ethical, clinical and legal validity – some arguing for their dismissal (18); other deploying more moderate arguments still based on questioning the value of RTT laws, but recognising their intent and the importance of improving regulation and access to experimental medical products, and of addressing the communication gap between experts, who oppose the laws, and the public (19). We managed to find only one paper in the scientific literature which endorsed RTT laws (20). Therefore the arguments in favour of the RTT laws presented in the section 3 below are principally extracted from the Goldwater Model legislation (21), the RTT webpage (http://righttotry.org/about-right-to-try/), grey literature, and from the critical papers.

3. The main arguments in favour of RTT laws

The justifications for the RTT laws touch on the ethical principles of autonomy, beneficence, and justice, and so the main arguments used by their proponents can be summarised in the points below.

3.1. RTT removes regulatory walls

RTT laws are underpinned by a strong neoliberal framework. Central to these laws is patients' right to life and to choose (with the involvement of HCPs) any experimental medical products that might prolong their lives without the mediation of governmental/regulatory bodies such as the FDA. Despite the efforts made by FDA to ease and speed the process of EA (see section 1.1), for RTT advocates EA remains an unnecessary and burdensome bureaucratic barrier that can delay access to experimental medical products. RTT is also a play on 'right to die' i.e. terminally ill patients' right to request lethal prescriptions. Some proponents of the RTT claim that it is inconsistent that

in some US states and other countries a patient has the right to take a lethal drug – by definition, with 100% probability of being unsafe – but does not have the right to try an experimental treatment with less than 100% probability of being unsafe and ineffective. Thus, these proponents claim that the RTT is embedded in the right to die (20). They see the right to die and right to life as two fundamental expressions of individual autonomy.

3.2. RTT laws allow a timely access to experimental outcomes

RTT proponents claim that medical products which have passed Phase 1 of clinical trials are already safe enough for patient consumption, or at least safe enough to give some hope to terminally ill patients. They often depict the FDA's concern to ensure sufficient levels of safety and efficacy of the experimental medical products as mask that delays or prevents terminally ill patients from doing all they can to try to prolong their life. RTT advocates claim that applications for EA through FDA are time consuming for both HCPs and patients, placing an unnecessary burden on vulnerable terminally ill patients who have limited life expectancy (and are therefore pressured for time).

3.3. RTT laws reduce inequalities

RTT advocates claim that the laws rebalance access to the therapeutic benefit of experimental medical product in favour of terminally ill patients who tend not to be eligible to RCT, and in other circumstances e.g. if the medical products not approved by FDA are available in other countries. In this case not all patients willing to try these experimental products have the ability to travel/ move to these countries.

3.4. RTT laws improve patient-HCPs communication and decision making

For RTT proponents the laws enable patients to discuss with HCPs more therapeutic options. The so called 'out of options talk' in oncology (and other end of life care situations) is difficult for both patient and HCPs. RTT would postpone or avoid such difficult conversations offering instead more options and hopes to terminally ill patients.

4. The main arguments against RTT laws

The ethical principles of autonomy, benefice and justice are also key to the critics of the RTT laws. Nevertheless, critics tend to highlight two important weaknesses in these laws: an insufficient consideration of the tenuous nature of the development of new medical products, and an insufficient consideration of individual and public interests. The main arguments against RTT laws are summarised below.

4.1. Formal vs substantial right

RTT laws suggest that experimental medical products will be easily available to patients who request them (or more easily than FDA's EA). However, the rights they confer to patients are only *formal*, and not *substantial*. The laws prevent the FDA from interfering with access to experimental products in the case of eligible patients, but they do not impose a positive duty on the manufacturer to make their products available (19). Thus, the decision about access rests on the company, and many companies are not inclined to grant access due to several factors, including:

- Pre-approval access requires considerable effort (organisational, logistical and financial) and would limit the availability of the experimental product for the clinical trial, which is their higher priority.
- Pre-approval access may slow the RCT and the final approval, harm the clinical trial, and even jeopardize the chances of approval.
- If a terminally ill patients develops adverse effects, this may generate bad publicity possibly affecting the eventual profitability of the drug, and in the worst case the survival of the company (22).

The fact that RTT laws absolve producers from legal liability from any harm the experimental medical product can cause on patients may help, but does not address the above concerns. On the other hand, it is worth recalling that under FDA EA, companies must first agree to provide the experimental product to the patient. Although the FDA cannot oblige the company to make the experimental product available outside RCT, the FDA often works with the company to avail the medical product to the patient (9) – contributing therefore toward a more *substantial* form of right to patients than RTT laws.

Therefore, the RTT laws can create an *expectation or illusion of access*. Contrary to the RTT laws' idea of the FDA being a regulatory wall, the real gatekeeper for access to experimental products can be the manufacturer. Obtaining the drugs from the producer is often more difficult than getting EA approved by the FDA (18).

Some critics have also questioned whether RTT laws would even confer a formal right to patients. In the current federal law, the FDA regulatory apparatus is constitutional, and this would pre-empt RTT state laws, which aims to bypass the FDA (23, 24). Moreover, while some proponents of RTT laws may still expect states independence from federal

FDA regulation of experimental medical products on a patient-by-patient level (14), it is unlikely that such independence would be kept in a public health emergency (e.g. a disease outbreak) which may require a multi-state coordination of the procurement and distribution of a large quantities of experimental medical products (15).

From this perspective RTT laws appear to be a largely symbolic attack to the governmental authority of the FDA, masked by a libertarian ethos of conferring more rights to patients, but without any positive measures to guarantee these rights and autonomy.

4.2. Inequalities

Even if the company decides to grant access to the experimental product they are developing, there is another important consequence of the formal nature of right conferred by RTT laws. If the company makes the product available, it can decide to charge the patient, and health insurers may not reimburse such costs. RTT laws do not provide financial support to patients seeking access (although there are some exceptions, e.g. Utah established a private foundation to address this concern; Texas RTT laws require the pre-approval medical product to be provided for free (25)).

Patients may be personally responsible for paying for the experimental agent. Therefore RTT laws may reinforce pre-existing inequities: patients with financial means (who may also have more time, resources and educational skills needed to navigate a challenging healthcare system) are more likely to have greater access to these experimental treatments (26). They may also divert HCPs' time, attention and resources from patients who are more burdened by disease personally or in their family, living in poverty, less articulate or less educated, have cognitive impairment. This would contribute to an inequality whereby less needy patients would receive more attention from HCPs than those who have more needs, as per Tudor Hart's Inverse Care Law (27).

It is also important to highlight that RTT laws present significant inconsistencies across states on what constitutes 'terminally ill', and these inconsistencies create both confusion and increase inequalities. For example RTT laws provide no directions for HCPs and patients in the case of a patient living in a state but receiving cures from an hospital in a different state with different definition of 'terminally illness' or other variations of RTT

laws when it comes to insurance or financial coverage for the experimental medical product.

Another form of inequality stems from the RTT use of terminal diseases as eligibility criteria. These criteria exclude patients with serious but not life-threatening conditions e.g. those with degenerative diseases, untreatable depression, and chronic conditions. Eligibility criteria for EA are broader ("serious or immediately life-threatening disease or condition"[6]) and also include patients with serious conditions.

4.3 Speed vs safety

Many critics have expressed concerns that the RTT laws prioritise speed and downplay safety. The laws minimise the risk of taking experimental medical products, potentially exposing terminally ill patients to unnecessary harm. Many experimental products that complete Phase 1 trials fail to receive FDA approval because in later phases of the trial they are found to have serious side effects (or to be ineffective). Notably, potential adverse events of experimental products are normally not known up to and including Phase 3 of RCTs. It is not surprising that a 2014 study shows that approximately only one in ten experimental medical products makes it through the FDA process and its approval for clinical use (28). Thus, the harm caused by experimental treatments accessed through RTT can often exceed the potential benefit (9). Advocates of RTT laws appear to overestimate the benefit that might be obtained by a new and still experimental treatment. Moreover they ignore the tenuous nature of the development of medical products .

Other ways in which RTT laws can threaten patient safety have also been highlighted. Most versions of RTT laws do not establish a threshold of qualification for the HCP diagnosing the terminal illness in the patients or the HCPs/researcher recommending the experimental medical product. This may negatively affect the diagnosis of patients' conditions, the prognosis and the assessment of the risk and benefits of the experimental medical product. It may also expose terminally ill patients to 'experimental cures' which are not validated by scientific evidence (18).

Moreover, these laws may take health benefits away from patients. In some states,

[6] https://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm20041768.htm

patients who use an experimental treatment may lose their right to hospice care, home health care, or insurance (29, 30).

Arguably this 'speed over safety' issue reveals a contradiction in RTT laws. The laws appear to trust (or rely on) medical research to the extent that even its early stage experimental *products* are worth trying as they may be beneficial – but at the same time they do not trust the *process* used by medical research to test and develop such products.

4.4. Individual vs public interest

RTT laws raise ethical and regulatory questions about the equitable balance of individual and public interests. A fundamental question is whether and to what extent producers and research teams should re-direct experimental products and resources from RCTs to individual patients, and how this should be financed. Granting access to individual patients for experimental medical products may compromise the set up and completion of the RCT that would ultimately benefit a larger number of people.

As discussed above, RTT may facilitate the use of experimental medical products that are contraindicated especially to more vulnerable patients. Even if patients with life-threatening conditions may be willing to assume the risk of taking experimental and potentially contraindicated medications, the adverse outcomes they may develop (adverse outcomes are more likely in terminally ill patients compared to eligible RCT participants) could delay or even derail the eventual approval of the product. For example, they may discourage companies from proceeding with the RCT or they may lead the FDA to deny approval.

Those who claim that RTT laws are embedded in the right to die disregard the fact that, unlike the right to die situation, the consequences of access to experimental treatment in a RTT context has direct negative implications for RCTs and general public health interests.

4.5. Patient-HCP communication

RTT laws require patients to give informed consent, principally based on HCPs' description of best and worst outcomes of using the experimental medical product. An assumption of these laws is that patients and HCPs have reasonable access to information about risks and benefits of taking an experimental medical product. This assumption and

the idea that patients can provide informed and voluntary consent under RTT laws has been strongly criticised.

There is normally scant information available about the safety of medical products that have completed Phase 1, and clinical data about RCT is often unavailable to HCPs and patients (31). Therefore, HCPs who are asked to take informed consent may not be able to give patients meaningful information about the risks and benefits associated to the experimental medical product. This is a serious problem given that, as discussed previously, experimental medical products are likely to worsen the patient's (medical, psychosocial and financial) condition.

Critics have focused not only on the *quantity* and accuracy of the information available to terminally ill patients, but also on its comprehensiveness, or *quality* (32). Some critics have expressed concerns that RTT laws (and also EA) may limit the scope of HCPs-patient interaction, and consequently patient decision making, placing too much emphasis on intensive forms of treatments, at the expense of other important clinical options such as palliative and hospice care. Palliative care focuses on improving quality of life, it can increase life span, it can be provided concurrently with treatments, and is more effective when administered early in the course of the illness (for example, the American Society of Clinical Oncology recommends early prescription of palliative care (33)). Clinical options that may improve the quality of life, and potentially life-spans such as palliative care may therefore be relevant to the needs and values of patients. Such options should be discussed with patients, and – also in a hypothetical context of RTT or EA – should be part of the consent process. However, discussions about palliative care do not appear to be common in the USA context. In recent studies, 80% of Americans reported not to know what palliative care is, and both patients and providers often viewed palliative care as a sign of 'giving up'(26).

This is linked to other important ethical aspects of informed consent: the voluntary nature of request, and the absence of coercion and undue influence. In the USA (but also in other countries) there are strong social norms and expectations of maintaining a 'fighting spirit', keeping a positive attitude, or regaining power and control in the face of serious chronic or terminal conditions. These norms and expectations can have a negative impact on patients' understanding, management and experience of illness (34). In the context of end of life care, HCPs can feel pressure to describe prognosis and benefits of

experimental treatments over-optimistically (or simply to avoid mentioning other options such as palliative care). At the same time terminally ill patients, and their families, can feel pressure to pursue intensive treatments 'hoping to get better', but instead potentially compromising the quality and length of their lives (35).

This problem is also linked to the ethical concern of therapeutic misconception i.e. terminally ill patients – and more broadly any participant to medical research – may overestimate the benefit that experimental medical products can grant them. For example, some patients seeking RTT may believe that by having access to experimental medical products before their approval they may accelerate the completion of the RCT, helping not only themselves, but also other patients with similar conditions as well as future generations.

End of life care should be a bidirectional process between patient and HCPs characterised by the communication of relevant information in a way that can help informing patients decisions i.e. flexible to the needs of the patients (36). This implies that the information provided should be comprehensive, covering more options than the 'intensive treatment focused' EA or RTT ones, and include for example palliative care.

In the case of patients and HCPs deciding to access experimental medical products, consent should cover an adequate disclosure of risks and benefits associated with the product – or lack of information thereof. This should include considering the financial aspects such as the purchase of the experimental product and payment for the management of medical condition associated with the use of the product. The discussion of risks should also include, if appropriate, the loss of hospice care due to use of experimental treatments. Finally, patients should be informed that access to experimental medical products outside RCT may compromise the development of the treatment for larger numbers of patients in the future.

The EA programme has some measures in place to create conditions for informed and voluntary consent, therefore ultimately safeguarding individual autonomy more than RTT laws. For example the FDA receives updates after each phase of the clinical trial, and has information most HCPs do not (37). Moreover, the IRB is tasked with verifying that the consent form is accurate and that consent is voluntary (29, 30). Some critics have also suggested that in both EA and RTT contexts, psychiatrists or other 'health coaches' should be involved with assisting patients and HCPs to enhance communication skills

and decision making in important areas such as discussing prognosis and clinical pathways (17, 26).

There is a form of 'historical irony' in RTT laws. Arguably RTT laws represent the current stage of a process of reframing – in an opposite vein – the conditions of patient consent to treatment and to participation in medical research. This reframing is counter to the concern – addressed by the development of informed consent – of protecting individuals from harm and risks associated to medical research and practice. Informed consent was a reaction to the scientific abuses conducted particularly during the Second World War and some medical research in the post-war period on human subjects, who were not aware of the procedures they were undertaking. It entails that HCPs and/or researchers have to take reasonable care to ensure that the patient is aware of material risk involved in the recommended treatment or participation to research (38). Within the RTT laws framework, the 'protection' of individual autonomy 'stretches back' to the idea of participating to early stages medical research when benefits, safety, and risks are unknown.

5. Discussion

RTT laws are specific to the American normative system, and would need to be significantly modified in order to export them to a different country. Nevertheless, something ethically relevant –and still 'universal' – might be learned from them, and from the consequent debate.

There is an aspect in the RTT laws that may be certainly considered morally plausible, i.e. they place emphasis on the question of whether and how terminally ill patients should have timely access to experimental medical products. This aspect has to be taken into account when we morally weigh their content. The diverse international efforts to make medical products available before the completion of RCT appear to corroborate the relevance of this aspect. Yet, our review has shown that there are other aspects of the RTT laws that pose some problems to their moral plausibility.
To begin with, the rights they confer are *formal*, and not *substantial*. Not only because the procedure to obtain access to Phase1- medical products could be difficult, but also because the cost of the potential product is usually charged to the patient. This creates an unfair situation and economic inequalities, since only those who are affluent enough can have the substantial right to access these potential treatments.

Moreover, there is the issue of the lack of information about the side-effects of medical products which have passed Phase 1, which clashes with the RTT laws' requirement that the requesting patient (or designated guardian) should give informed consent. We have also argued that there is a contradiction in RTT laws: they trust (or rely on) medical research to the extent that even its experimental products are worth trying as they may be beneficial – but at the same time do not trust the process and regulations medical research adopts to test and develop such products.

Finally, we need to consider the relevant conflict between the potential interest of the terminally ill patient, and the public interest related to RCTs. To access an experimental medical product before the conclusion of a RCT could delay or derail its approval. This could harm present and future patients who may benefit from the RCT.

Addressing all these problems is very challenging and requires a multifaceted strategy. Below we will suggest a multi-pronged strategy which blends ethical tools (already discussed within the bioethical community) aimed at improving the communication between HCPs and terminally ill patient, and some considerations to address the boarder social challenges that surround the RTT debate.

5.1 Ethical tools

'Trusted' Consent. As discussed previously, a truly informed consent to access an experimental medical product which has passed Phase 1 can be difficult to achieve, as it is too early to know the possible benefits and side effects of the product. Different models of consent have been proposed in both clinical and research settings to overcome the problem of lack of information. This includes for example the context of research biobanks, in which the information provided to the givers – especially information concerning the secondary use of their samples – cannot be complete. The main idea proposed is a model of consent based on the concept of 'trust' (39-42) whereby consent is envisaged as a *process,* a bidirectional consultation between HCPs/researchers and patient/participants that goes beyond providing information (as per the traditional form of informed consent), but that is aimed at communicating values (i.e. the values of the HCPs/researchers and their instructions) and enabling choices. Such model is more realistic in contexts where it is not possible to access or there is not all the 'relevant' information required for a fully informed consent. This model is in line with the idea of

promoting an *ethics of uncertainty* (43), based on reciprocity between patients/participants and HCPs/researchers, and on co-producing decision making tailored to the patient/participant. Such model of consent based on trust may be both more achievable and suitable (than 'informed' consent) in the context of access to investigational products for terminally ill patients. However, we have seen that there may be other clinically viable options available to terminally ill patients besides access to experimental treatments. Therefore, something that *precedes* (and may or may not lead to) the trusted consent process may be needed to ensure that the communication between HCPs and terminally ill promotes decisions centred on the needs of the patients.

Ethical Counselling. The second tool regards the possibility to introduce an ethical counselling service to improve end of life care and decision making. This tool could be available to the patient and to the HCP before the decision to request access to investigational medical products. The ethical counselling framework developed in Europe by Boniolo et al (44) is particularly suitable to this scope as it aims to improve decision making by helping *both patients and HCPs* to navigate complex clinical and ethical options, and by supporting choices that promotes patient autonomy i.e. decisions that are informed and in line with patients' *personal philosophies*. The term *personal philosophy* refers to the: *"wide set of more or less deep, coherent and justified metaphysical, methodological, religious, political, esthetical, ethical, etc., beliefs, assumptions, principles, and values that an agent possesses and that characterises in a unique way how he/she approaches the world and life. […] (T)he 'conceptual and value-laden window' from which any individual starts reflecting in order to make judgments, to make choices, and to act",* (44:p. xiii). Such ethical counselling approach would help terminally ill patients and HCPs to evaluate the information and options available and consider the implications of different choices. This would often include balancing the risks and benefits at individual (safety, costs, quality of life) and societal level (impact on RCT, public health), thus addressing most key concerns expressed by both sides of the RTT debate.

Most aspects of the conflicts between individual and public interest, between individual autonomy and regulation of clinical research that can arise in the context of end of life care and RTT cannot be solved a priori, but require to be addressed on a case-by-case basis. Patients have different cultural backgrounds and needs; clinical options are also diverse, and can vary depending on the patient condition, priorities, clinical and other

contextual factors. There is also another important observation to make. The fact that the harm caused by experimental treatments assessed through RTT can often exceed the potential benefit (see section 4.3), challenges the very existence of a 'conflict' between individual and public interest.

In the absence of a *substantial* individual interest, the 'individual/public' conflict disappears, and what remains is the potential public interest in continuing a clinical trial. The RTT issues are underpinned by a strong libertarian view of individual autonomy whereby individuals are construed as self-sufficient, self-directed 'atomic' agents, capable of making independent decisions when informed. However, individuals are immersed in a complex network of relations and interdependencies. Applied to the context of medicine this means that illnesses are inextricable blends of biomedical information (sometimes incomplete), filtered through individual (the personal philosophy) and relational aspects (what has been called the *lifeworld*) (45). There are other ways to conceptualise autonomy that better approximate to this complexity, and that are conducive to promote choices aligned to the values and desired outcomes of the individual patient. There is an obvious need for a conceptualisation of autonomy that considers both internal factors (e.g. levels of understanding of medical information that is a disposal), and external factors (e.g. cultural social influences, income, vulnerability, emotional needs) that may influence patient understanding of information and decision making.

This ethical counselling framework just outlined is in line with both the relational view of autonomy which recognised that individuals are immersed in a network of relations and interdependencies (41); and with research conducted on patient-HCPs communication in end of life care, e.g. truth disclosure in oncology (46, 47). It offers some safety measure to protect patients from paternalistic medicine, therapeutic misconception, and to empower both vulnerable and more assertive patients. This is because: i) it is patient-centred and aims to improve decision making by placing emphasis on the communication of the relevant information in a way that is tailored and responsive to patients' personal philosophies and needs, and can inform the decision of the patient accordingly; ii) it takes into account possible cultural variations in relation to how to convey information, when, and how much; and iii) it is aimed at *both patients and HCPs*.

5.2 Points to consider

We recognise – together with some critics of RTT laws – that the social challenges touched by these laws extend beyond the HCP-patient interaction. Hence, we present below three other points that deserve to be discussed.

Stakeholder Engagement. The needs of terminally ill patients should not be underestimated. However, rather than bypassing the scientific and regulatory authority of the FDA, as the RTT laws do, it is important to identify and engage the stakeholders of medical research (e.g. patient advocates, producers, HCPs, health regulators and authorities, ethical counsellors, and bioethicists). That is, before implementing a RTT regulation (at whatever level it could be) it seems necessary to realise a good deliberative process (48-50) among all the stakeholders. This could provide a legitimate (by the deliberation itself) draft of the bill to be submitted to the legislative authority. In such a way the needs of all the stakeholders would be considered and the legislator could arrive at regulation that could satisfy all the parts involved (51).

Information and education campaigns. There are many challenges with designing genuine (as opposed to tokenistic) stakeholder engagement (52). A useful step would be to improve media information and education campaigns about the complex field of clinical trials (53), the tenuous nature of the development of medical products and the negative impact that unregulated access can have on individual patients (e.g. some patients have shorter and more miserable lives as a result of trying experimental medical products) and on public health. This will contribute to filling the 'gap' between experts and the public (7, 54, 55), having also a positive impact on the HCP-terminally ill patient clinical encounter.

Cost considerations. RTT or similar programmes should not damage the capacity of a research team and/or clinical service to deliver other key ethical imperatives, e.g. offering equitable clinical care, or conducting medical research. Therefore, we press that any stakeholder engagement and communication endeavours should promote to changes in RTT, EA or any other programme with similar aims, that do not increase economic unfairness and inequality.
As shown (see section 4.2), the RTT laws, as they are now, can increase inequalities. On the one hand, there is the company's request to be paid for the medical product it is developing, and for which it has invested money and resources. Moreover, RCTs have

finite resources and a terminally ill patient request may shift research teams' time and resources from conducting their RCT towards monitoring individual terminally ill patients who are not part of the RCT (and managing potential complications they may develop).

On the other hand, there are patients who can afford the cost and those who cannot. In theory, it is unfair to both deny the potential treatment to patients who cannot afford the cost, and to deny those who can afford the cost the possibility to access the investigational medical product.

A compromise should be found to properly substantiate the RTT or any similar programme. One possibility could be to establish a charity (or leverage already existing charities) to offer financial support to terminally ill patients who are not affluent and could receive benefit from the investigational medical product under RCT (this idea is similar to the private foundation established in Utah, see section 4.2).

There is also the possibility that those who request access to the experimental medical product and are affluent could pay the cost of the product, alongside with a fee given to an institution which will use that money to support less economically affluent terminally ill patients. This fee could be justified not only on the basis of reducing inequalities of access i.e. on the ethical principle of justice, but also on the principle of reciprocity. Patients requesting access to experimental medical products should in fact to consider those who have been enrolled in the Phase 1. The fee could represent a 'reward' (which is available to other requesting patients) for what the participants to the clinical trial have given to the requesting patient: the possibility to use a Phase 1 approved treatment. This is a typical solidarity open ring: *I take advantage of the solidarity of the volunteers enrolled in Phase 1, and someone else takes advantage of the fee that I pay over the cost of the potential treatment*.

6. Conclusions

There is prevalence in the literature of arguments against RTT laws. This is at odds with the popularity of these laws and reflects a communication gap between the so-called experts, who oppose the laws, and the public.
In this paper we have assessed the ethical plausibility of these laws. We have taken a moderate approach – in line with some of the literature – based on recognising that RTT

laws have contributed to raising awareness about the need to improve end of life care, but that they do not provide effective means to achieve this aim. This is largely because they tend to reduce the complexity of end of life care and the needs of terminally ill patients to issues of access to experimental medical products (and they also propose to do so in an ineffective way). However, whilst such issues might be relevant to some terminally ill patients, and in certain circumstances, there are other equally important aspects – related to the safety and choices of terminally ill patients, and to the rights and perspectives of other stakeholders – which are dangerously overlooked by these laws.
On a conceptual level, we have identified a sort of contradiction in RTT laws. They trust (or rely on) medical research to the extent that even its early stage experimental products are 'worth trying' as they may be beneficial, but at the same time they do not trust the process used by medical research to test and develop such products. This is revealing of what we have referred to as a form of 'historical irony' whereby RTT laws represent the current stage of a process of reframing – in an opposite vein – the conditions of patient consent to treatment and to participation in medical research.

On a more practical level, we have suggested a multi-pronged strategy based on a set of complementary ethical tools and considerations which might help to address most of the concerns raised by both sides of the RTT laws, respecting the interest and needs of the main stakeholders.

Acknowledgments

This paper was funded by the European School of Oncology.

Conflict of interest
The authors declare no conflict of interest

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