Uncertainty and certain death: the role of clinical trials in terminal cancer care

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Abstract

We consider uncertainty in relation to clinical trials for terminal non-small cell lung cancer, which is an aggressive and difficult to treat form of cancer. Using grounded theory to analyse 85 clinical interactions between doctors, patients and family members, we argue that uncertainty is a major source of tension for terminally ill patients, with individuals confronting a choice between transitioning to palliative care or volunteering for an experimental/trial medication that might postpone death. Regardless of their efficacy, patients must also consider how such experimental treatments might impact their quality-of-life. We argue that clinical trials produce uncertainty through (i) discussions about the efficacy of clinical trials; (ii) the physiological consequences of clinical trial medications; and (iii) the impact clinical trials have on patient’s prognostic understanding of their terminal cancer. Accordingly, while study participants encounter high prognostic certainty (i.e. they have a fatal cancer), they nonetheless experience considerable uncertainty in relation to their participation in clinical trials.

Keywords: uncertainty and risk, clinical trials, end-of-life care, lung cancer, health and illness, prognosis

Introduction

Developments in science and technology are consequential for professionals, patients and caregivers. Numerous social scientific studies have investigated the impact of such medical science developments. A central tension in this literature is that biomedicine is simultaneously associated with risk and uncertainty on the one hand (Clarke and Shim 2011, Clarke et al. 2010, Hofmann and Svenaeus 2018, Sulik 2009), while connected to precision and control on the other (Clarke et al. 2010, Conrad 2007, Joyce 2008, Sulik 2009). Indeed, the tensions between precision and uncertainty are evident within discrete studies and frameworks (Armstrong 1995, Clarke et al. 2010, Rose 2007). The tensions between precision and uncertainty are the focus of our analysis of non-curative clinical trials.

Cancer kills more people worldwide than any other disease and is the second leading cause of death in the United States (Siegel et al. 2018). An estimated 1.68 million cases of cancer are identified each year in the US, with lung cancer accounting for 25–30% of all cancer deaths in the country, which is more than the next three types of cancer combined (American Cancer Society 2016, Lindeman et al. 2013). Lung cancer is generally classified into two...
classes, non-small cell lung carcinomas (NSCLC) and small-cell lung carcinomas (SCLC). Non-small cell lung cancer, the focus of this article, makes up the majority (approximately 85%) of these lung cancer cases.

Cancer treatment is intimately linked with research (Fujimura 1996, Keating and Cambrosio 2012). In the last 10 years, there has been a 61% increase in the number of oncological clinical trials initiated worldwide (U.S. National Library of Medicine 2019), with the United States operating as a major hub for experimental cancer medications (Hirsch et al. 2013, U.S. National Library of Medicine 2019). In the United States, sponsoring companies (e.g. pharmaceutical companies) often cover the cost of medications, laboratory tests and diagnostic scans associated with the clinical trials. Additionally, the Patient Protection and Affordable Care Act, often called ‘Obamacare’ (statute 42 U.S.C.A § 300gg-8 under PPACA Section 2709), mandates that insurance companies must cover routine care costs for trial participants. While terminal lung cancer patients have increased access to medications, evidence suggests that end of life treatment is associated with worse quality-of-life (Dalal and Bruera 2017, Zhang et al. 2009), and that many clinical trials and experimental treatment options fail to extend life.

In this article, we argue that clinical trials produce medical uncertainty in the context of terminal cancer. All the patients in our study encounter high prognostic certainty, as they have all been told they have terminal cancers. Nonetheless, we argue that patient–doctor interactions regarding clinical trials produce uncertainty through the use of precise and quantitative language (Efficacy), the unknown impact of trial drugs (Treatment Consequences) and the potential for trial treatments to eliminate patients’ cancers (Prognosis). Our argument here is not to observe that clinical trials are risky, experimental or uncertain but that patient–doctor interactions surrounding clinical trials dissolve, mitigate or challenge the certainty of a terminal diagnosis. Our argument is also not about the discrete medical products (e.g. a trial drug) but the interactions that surround such products. After demonstrating how clinical trial interactions produce uncertainty, we discuss how our findings might guide future analysis of medical uncertainty regarding patient–doctor interactions and the clinical care of terminally ill cancer patients.

Literature review

Macro sociological theories suggest that uncertainty and risk are central elements of both modern social structures and experiences (Beck 1992, Giddens 1990, 1991). That is, increasingly complex technological breakthroughs, fragmented knowledge systems and consumeristic market-based economies create environmental risks and threats to social order. These features of modernity disrupt identities and destabilise self-perceptions. While numerous scholars question the conceptual and analytic utility of risk and uncertainty (e.g. Alexander and Smith 1996, Dingwall 1999, Green 2009, Mythen 2005, Scott 2000), we consider how clinical trials produce uncertainty in the context of terminal cancer. However, in doing so, our work also contrasts macro theories of risk and uncertainty (e.g. Giddens 1990, 1991) as our focus is on how uncertainty manifests during patient–doctor interactions. Uncertainty is also a central element of social scientific theories and studies of health (Clarke et al. 2010, Davis 1960, Fox 1957, Rose 2007, Sarangi and Clarke 2002). More relevant to our study, there is renewed interest in relation to the institutional management of medical risk and prognostic (un)certainty (Brown 2013, Pilnick and Zayts 2014, Sarangi and Clarke 2002, Skinner et al. 2018). While doctors might struggle to discuss prognostic uncertainty (e.g. estimated life duration) with terminally ill patients (Schuster et al. 2012), studies also suggest that physicians avoid commenting on such prognostic uncertainty, as they might be poorly evaluated for making errors (Christakis

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and Iwashyna 1998). Complicating these challenges faced by physicians, research also indicates that both prognostic certainty (Halpin 2018, Konrad 2005) and uncertainty (Nettleton 2006, Timmermans and Buchbinder 2010) are distressing for patients.

In the popular media (Morrissey 2019), emerging technologies and the associated development of personalised medicine are positioned as a means of alleviating medical uncertainty. While developing technologies provide opportunities to quantify, test and measure, social scientific research suggests that such technologies might (Reed et al. 2016) or might not alleviate prognostic uncertainty (Fox 1980, Pilnick and Zayts 2014, Sulik 2009). Rather than resolving uncertainty by revealing an ‘objective’ or ‘real’ phenomena, sociologists of science suggest that new technologies often create or translate controversies and debates (e.g. Garfinkel et al. 1981, Joyce 2008). Indeed, Collins (1975) suggests that scientific debates and uncertainty can only be resolved by social, rather than technological, means. Engaging with this debate, we argue that emerging trial drugs disrupt the certainty of a terminal cancer diagnosis. Our concern here is not the materiality of the trial drugs but instead the interactions and micro-processes surrounding such medical encounters (see also Littlejohn and Kimport 2017, Stivers and Timmermans 2016).

As numerous scholars have observed, medical risk and uncertainty are primarily expressed in quantitative terms (Fosket 2004, Greene 2007, Rose 2007). Indeed, such quantification is central to major conceptual work in medical sociology, such as biomedicalisation theory (Clarke et al. 2010) and studies of surveillance medicine (Armstrong 1995). That is, health and illness are increasingly communicated via percentages, odds ratios and relative risk. However, research in numeracy—the ability to understand numbers and mathematical concepts—shows that patients do not respond such numerical representations well (Fagerlin and Peters 2011, Peters et al. 2007). Patients not only report difficulties understanding highly quantitative health information, they also have difficulty recalling quantitative information even when it is initially understood. Once again, employing an interactionist perspective, we consider the relationship between precision and uncertainty by examining both the medical language and probabilistic terminology surrounding patient–doctor interactions about clinical trials.

In a landmark study, Glaser and Strauss (1965) argue that becoming aware of your death is a process. Terminal patients move through four stages of death awareness, transitioning from a lack of knowledge about their death (closed awareness) to being explicitly informed their condition is terminal (open awareness). Revising the death awareness concept, Timmermans (1994) argues that Glaser and Strauss overemphasised information and the perspectives of health professionals. Contrastively, Timmermans asserts the salience of emotions and the perspectives of patients in relation to death. Timmermans also parses open awareness into three phases, wherein patients move between ignoring information about their death (suspended open awareness), focusing solely on the potential positive outcomes (uncertain open awareness) and explicitly accepting their terminal situation (active open awareness). Our article brings an interactional perspective to death awareness and, like Timmermans, we revise the concept by arguing that science, technology and biomedical language modulate open awareness.

Methods

Data for this article are obtained from 85 clinic visits involving 65 lung cancer patients. Visits lasted between 12 to 69 minutes (M = 22). After obtaining clinic and university ethics approval, the first author (FA) observed interactions at the ‘Lorne Cancer Center’ (all names are pseudonyms) housed in an American university hospital. The FA observed and digitally
recorded every interaction. Audio files were transcribed verbatim. Ethnographic field notes (Emerson et al. 1995) documented conversations before and after clinical encounters, as well as non-verbal actions (e.g. doctor drawn diagrams). Recordings occurred in examination rooms, while observations additionally occurred in the clinicians’ workroom—a large room closed off to the public in the middle of the clinic that oncologists used to look at scans, review patients’ charts and prepared for clinic visits.

All participants had either public (e.g. Medicare) or private insurance. While American health care can be cost-prohibitive, trial medications are covered through a combination of government regulation and corporate payment (reviewed above), and no participant cited cost as a factor in their clinical trial decision-making. Indeed, in our dataset, doctors discuss medication cost more than patients. Participants include 65 lung cancer patients (35 female, 30 male), 48 family members (26 male, 22 female), three oncologists (two female, one male), five nurses (all female), three medical assistants (one female, two male), four medical residents (all female) and one clinical trial liaison (female). Consistent with grounded theory (Charmaz 2006), participants were purposively sampled, a sampling strategy that aims to select information rich cases (Patton 2014). More specifically, the FA employed criteria-based sampling (Palinkas et al. 2016) by selecting adult participants who were diagnosed with incurable NSCLC (stages III-A, III-B, IV-A or IV-B) and were attending the Lorne Center.

As data collection advanced, the FA also used theoretical sampling, which selects cases to develop, clarify or challenge emerging observations (Charmaz 2006). Specifically, the FA noticed instances wherein patients discussed ‘curing’ their cancers, with such conversations often attending to non-curative clinical trials. Coordinating with Lorne Center clinicians, the FA adjusted his sampling strategy to ensure that he recruited a subsample of patients who were discussing non-curative clinical trials and were present for appointments with patients who had previously consented and were reviewing non-curative trial medications. The trials in this articles were either double-blind, blinded or non-blinded. Some trials were single-arm, meaning patients knew if they received the drug. None of the clinical trials referenced in our data were curative. The majority of our analysis comes from the theoretically sampled cases (n=27); however, we draw on the analysis of the larger sample (n=85) to understand the organisation of cancer care at the Lorne Center.

During patient–doctor interactions, the FA was silent and unobtrusive, sitting in the corner writing field notes. The Lorne Center is a training hospital and patients frequently have medical students or various specialists sitting in during appointments and it was relatively easy for the FA to remain an uninvolved observer. The FA was more active before and after appointments, interacting with patients, caregivers and nurses. After appointments, the FA asked oncologists about the interaction in relation to their conversational approach, decision-making, treatment options and the interactional/emotional difficult of the conversation. Accordingly, the FA engaged in ‘shop talk’ while also observing ‘shop work’ (Maynard and Clayman 1991) to investigate cancer care interactions.

Audio files and field notes were coded using MAXQDA-18 software for qualitative data analysis. Initial coding of transcripts and field notes relied on line-by-line analysis (Charmaz 2006) with preliminary analysis leading to ‘focused coding’ as initial codes collapsed into new codes, and categories and themes emerged. This process also used a constant comparative approach (Charmaz 2006) facilitating comparison between different cases. Analytic memos were used to develop connections between codes and detail the relationships between (and among) categories and themes. Thematic analysis forms the basis for the subsequent findings section.
Findings

Our findings consider how clinical trials produce uncertainty in the context of a terminal diagnosis. Here, we are not detailing that experimental drugs themselves are risky, unpredictable, or uncertain (e.g. that they might have unknown or unknowable effects). Rather, focusing on in situ patient–doctor communication, we detail how perceptions of clinical trials are shaped via clinical interactions and how those perceptions influence the lived illness experiences of terminally ill patients. As such, we show how clinical trials produce uncertainty through the use of precise and quantitative language (Efficacy), the unknown impact of trial drugs (Treatment Consequences) and the potential for trial treatments to eliminate patients’ cancers (Prognosis).

The uncertain efficacy of trial drugs

It is necessary to establish the certainty of patients’ diagnoses before demonstrating how clinical trials might disrupt such certainty. In our study, patients have been explicitly and repeatedly informed that their cancer is terminal. Treatments are not curative, at best they slow the advance of patients’ cancers. For example, in a conversation with Kat (a patient) and Ben (patient’s husband), doctor Blackwell states:

I always indicate [to patients] that one option is to not use any anti-cancer drugs. To focus on your symptoms. At some point. When it is that we decide [that is] either you saying, “It’s not for me anymore.” Or I say, “I don’t think there’s any good options anymore.” Here the door is open to bringing more resources to you at home like hospice for example.

Dr. Blackwell reminds Kat that she will eventually exhaust her limited treatment options and, even before then, transitioning to hospice might be her best option. In this interaction, as well as many others in our dataset, death is clearly ‘on the table’. In contrast to Glaser and Strauss’ (1965) classic work on death and dying, doctors and patients in this study openly discuss death, and patients’ terminal prognoses are routinely mentioned. As such, all patients in this study are acutely aware of the severity of their diagnoses.

Our focus in this analysis is how interactions surrounding clinical trials disrupt this certainty and re-introduce uncertainty in the context of certain death. For instance, while Dr. Blackwell discusses hospice, he also suggests that clinical trials are ‘good options’ for Kat, modulating the certainty of her transition to hospice care. While death is ‘on the table’ for Kat, her transition to hospice care will occur at some ambiguous point in the future, after trial drugs cease working or Kat decides to refrain from treatment. Therefore, Kat has a certain prognosis (i.e. her cancer is terminal), but when she transitions to hospice care and what treatments she pursues are uncertain. As we argue throughout this article, patient–doctor interactions regarding clinical trials are one avenue for introducing such uncertainty in the context of certain death.

One means by which clinical trial interactions create uncertainty is via physicians’ use of probabilistic language to describe the efficacy of trial drugs. Medications ‘might or might not’ have an impact, the impact might be ‘modest’ or ‘substantial’, and ‘clinically significant’ improvement might occur for 10%, 20% or 30% of enrollees. Through this discourse, trials muddle the prognostic certainty of terminal illness, as patients might or might not be one of the few to receive ‘clinically significant’ results. For instance, Dr. Blackwell explains to Kat how one trial works:

When you give [drug one] to 10 people with lung cancer, it shrinks the cancer in two or two and a half of them. So roughly 25 people out of a hundred, 2 to 3 out of 10... That’s a better number, believe it or not than [drug two]. The number for [drug two] is closer to 10...
out of a hundred. This difference is meaningful, but actually the most meaningful thing is that when drugs like [drug one] work they tend to work for much longer than [drug two]. And so if you were to take those 100 people of those 25, somewhere around 15 or 20 of them get what we call a “durable response,” which might last months and actually sometimes it’s even measured in years.

Dr. Blackwell’s discussion of these trial drugs is characterised by probabilistic language as he reviews both rates of success and duration of response. Although couched in seemingly precise quantitative terminology, the impact either drug might have on a specific patient (e.g. Kat) are difficult to discern. If she takes the drug, Kat might be among the majority who experience no beneficial effects. She would also have to choose between the two trials, which covey different risks and outcomes. Additionally, Dr. Blackwell has previously discussed transitioning to hospice care with Kat (see above), while now presenting a drug that might provide a ‘durable response’ that is ‘measured in years’. In this sense, clinical trial interactions introduce uncertainty in the context of Kat’s prognosis, with her choices adding considerable complexity to when she might die.

In an effort to add some certainty to this discussion of probabilities, Kat and Ben ask Dr. Blackwell if there are genetic tests or similar techniques that might indicate if she will benefit from either drug before choosing a trial. Dr. Blackwell responds:

Well, no, you asked the perfect question. I mean, if you knew you were one of the 75% who it wasn’t going to work for then we could just avoid giving it to you. That would be lovely. Things like [test name] for example are attempts to try to figure out who’s that group, but the bottom line is “no.” We don’t have a good way of predicting who will respond and who won’t. Maybe someday we will.

Later in their interaction, Dr. Blackwell adds that, only after multiple rounds of treatment will he be able to know if a treatment is working for her, “we would do two rounds. So two months and then we [would] take a look…so basically four doses and then we get our scan.” Put simply, the only way for Kat to know if a drug works (or does not work) is to spend several months taking it.

As with the potential success rate, Kat similarly asks Dr. Blackwell to provide additional certainty in relation to the duration of the impact of the trial drug. Dr. Blackwell responds by explaining how the specific chemical agent acts in a body. Still unsure, Kat asks how the drug will impact her lifespan if she is not in the 25% who experience a benefit, “okay. And so if I’m not part of the 25%, then, um, do you have a sense of how much more? How many more months or whatever we get?” Dr. Blackwell tells Kat that if they see that the trial drug is ineffective then, “I think that probably makes it clear that time is measured in months.” However, Dr. Blackwell adds that he will not know how the drug might impact mortality until Kat takes it. Accordingly, although Dr. Blackwell provides a thorough review of Kat’s options, the probabilistic language surrounding trials produces considerable uncertainty: she might respond to only drug 1 or only drug 2, or she might not respond to either drug. If she does have a response, this might last months or years, substantial time for someone considering hospice care. Despite the medical statistics and novel technologies used to assess her progress (e.g. genetic tests, scans), Kat’s choice amounts to ‘trial and error’, with the difference between a correct and incorrect choice potentially being years of additional life.

As with probabilistic language, medical terminology also introduces uncertainty in clinical trial interactions, particularly in relation to how drugs might work. That is, when patients question physicians about the operation of a drug, physicians respond with extensive medical terminology that is simultaneously precise and inaccessible. For example, Luther (a caregiver)
asks Dr. Souza if there are non-invasive ways to produce lung samples required for a trial. Dr. Souza responds:

So, they just approved genetic testing of the blood for T790M. But in your case, we want to go beyond T790M. So, my impression would be that we would need to do tissue testing first to identify, well, what is the mechanism of resistance here? It’s possible that she still has the T790Mm, but something else is also popping up. I don’t know if you remember, when we first talked about your molecular results. You had the T790M mutation and you also had another one called the PIK3CA mutation, which is two resistance mutations. So, it may be that we’re suppressing the T790M and the PIK3CA is sort of now acting up. But we have no way of targeting both mutations at the same time because there’s no approved therapy that we can give that will target both mutations. So, that’s my guess that that might be what’s going on. But we’d only know if we really checked the tumor.

While many Lorne patients have considerable lay expertise (Epstein 1995, Wynne 1992) and Lorne physicians emphasise collaborative patient–doctor communication, Dr. Souza’s response is nonetheless embedded in a long list of medical terminology. Indeed, while Dr. Souza answers Luther, “we’d only know if we really checked the tumor,” the answer is embedded in extensive terminology that references specific mutations (i.e. T790M and PIK3CA), ‘mechanisms of resistance’, and ‘molecular results’.

The medical terminology in Dr. Souza’s response also includes some potentially negative news, suggesting that if both mutations (T790M and PIK3CA) are active, there is ‘no approved therapy’ that will help Luther’s loved one. That is, while they are discussing trial drugs, a lung sample might reveal that even trials Dr. Souza is aware of will not be of help. Further complicating matters, Luther receives all this information verbally, and without the benefit of the text we provide here. Indeed, the opaqueness of Dr. Souza’s response is indicated in Luther’s follow up:

Should we be waiting for the results of whether they’ll radiate her head? Or should we be searching the internet for clinical trials, or [are] you searching for clinical trials? Or let’s just wait to see what we’re gonna do with her head first?

Luther raises several potential courses of action, including waiting for more diagnostic information or searching online for clinical trial opportunities. Responding to this series of questions, Dr. Souza simply states, “I would do that first,” and the interaction has moved from a topic of relative simplicity (e.g. taking a tissue sample) to a situation wherein intervention options, their consequences and prognostic certainty are no longer clear. Accordingly, as with probabilistic language, the medical terminology that surrounds clinical trials produces uncertainty in the context of terminal cancer. And, despite the precision of Dr. Souza talk, Luther is left with more, rather than fewer, questions.

The uncertain consequences of trial drugs
Monitoring trial participants is labour-intensive at the Lorne Center, including laboratory tests (e.g. blood, urine and tissue analysis), questionnaires and diagnostic scans (e.g. neuroimaging). Despite extensive review and monitoring of adverse effects, the consequences of trial drugs produce considerable uncertainty for terminally ill patients. Accordingly, in this section we detail how clinical trial interactions impact how participants perceive the consequences of experimental drugs and experience biophysical risk.

Lorne physicians provide patients with extensive and careful reviews of potential trial drug side effects. For instance, Dr. Souza tells Richard (a patient) that a trial drug he is considering
can cause fatigue, blood clotting and a decrease in white blood cell counts. Richard asks if there is any potential of diarrhoea and neuropathy. Dr. Souza responds:

I would say about 10% to 20% [of patients develop neuropathy] so it’s an important one. It tends to be the more you get, the more the risk. So, it’s something that we just have to monitor and see if you have it. If you have it, then sometimes we need to, again, dose modify or change things around or stop it if it’s happening.

Although Richard’s interest in the trial partly hinges on his risk of developing neuropathy (and diarrhea), Dr. Souza can only provide estimates of his risk, adding that if he does develop neuropathy, it is likely to increase in severity throughout the trial. Resonating with our data above (Efficacy) and previous studies (see Fagerlin and Peters 2011, Lipkus and Peters 2009, Peters et al. 2009), Lorne physicians discuss these side effects in terms of probabilistic ranges and quantitative assessments. Although our argument is that such probabilistic language produces uncertainty, research also indicates that this kind of discourse might also operate as a distancing mechanism (e.g. Fagerlind et al. 2008, Helft 2005, Sandén et al. 2001). Here, a source of interactional uncertainty is a clinician’s inability to predict which side effect a patient might develop among a constellation of possibilities, and to what extent these side effects might impact their overall health. This uncertainty surrounding the trial side effects is further compounded by the already difficult task of explaining uncertainty to patients during clinic visits. That is, while patients are presented with broad knowledge on probabilistic outcomes, uncertainty surrounds their specific encounter with a drug, how it might impact their physiology, and how they might understand the risks and aims of clinical trials. In other words, the uncertainty surrounding the consequences of trial medications is not simply the product of the use of probabilistic language.

Not all of the potential biophysical reactions are known prior to a patient’s participation in a trial. Indeed, part of the work of clinical trials is distilling the precise adverse effects of medications. The opaque consequences of trial medications are apparent in an interaction between Dr. Blackwell and Kristen (a patient). Dr. Blackwell states Kristen has three options: palliative care, try the latest Food and Drug Administration (FDA) approved drug or enrol in a trial. He then lists the side effects of the experimental drug, including ‘bleeding because you are altering blood vessel growth and development’. Kristen is immediately worried about bleeding, asking “bleeding from where? Where? What, if you cut yourself? Will it come out my ears, nose, or mouth? Where? I mean, what kind of bleeding are you talking about?” Dr. Blackwell says it is difficult to tell, but previous enrollees have reported nosebleeds and blood in the gastrointestinal tract. Dr. Blackwell adds, “theoretically, you could bleed from anywhere. You have blood vessels everywhere.” Although Dr. Blackwell is able to list an adverse effect (i.e. bleeding) how, where and to what extent the drug causes bleeding is not currently known. Indeed, the experiences of potential enrollees (like Kristen) are necessary to ascertain the extent of such effects, in addition to whether the drug is useful in treating cancers. Despite her terminal diagnosis, Kristen decides the seemingly unspecified yet comprehensive possibility of bleeding is too risky in relation to her potential longevity and quality-of-life, and she declines to participate in the trial.

The interactional uncertainty surrounding trial drugs is compounded by the uncertainty of disease advancement, as a previously tolerable side effect can become unmanageable and hazardous as cancers change. For example, Sofia (a patient) decides to enrol in the trial that Kristen declines (see above). Through the first round of treatment, the drug slows the growth of her tumour, with both laboratory results and self-reports indicating no major side effects.
However, the latest round of diagnostic scans reveals the cancer has spread to her brain. For Dr. Souza, this development completely alters the drug’s risks:

I know it’s disappointing and I’m not, you know, I’m not downplaying. But I think safety first and because there isn’t enough safety data with this, when people have, you know, brain tumors and they’re worried about bleeding because this affects blood vessels... And it’s even possible, you know, that you’ve had this, and we just didn’t pick it up... So, I don’t think that you failed the regimen. The reason to stop it is for safety.

While Dr. Souza and Sofia were willing to navigate the side effects when Sofia first enrolls, the risks increase once Sofia’s cancer metastasises to her brain, which is a relatively common development for lung cancers (see Ali et al. 2013, Greenspoon et al. 2017). This case highlights how difficult it is to communicate the uncertainty and risk of clinical trials when also trying to account for cancer progression. Dr. Souza hints at this by expressing her surprise that the experimental drug stopped working and started hurting Sofia because the initial decrease “was more than I’m used to seeing. Throughout the visit it is clear that Sofia’s brain bleeding is unexpected, especially since the previous diagnostic scans and laboratory results showed the experimental drug to be working.

In the section above (Efficacy), we detailed how clinical trial interactions produce uncertainty by potentially delaying when a patient might die. Here, the consequences of trial drugs similarly produce temporal uncertainty vis-à-vis terminal diagnoses, as patients might die from the adverse effects of a cancer drug, rather than the cancer itself. While clinical trial interactions addressing side effects often revolve around probabilistic outcomes, these probabilities are transitory as cancer development intersects with drug effects to produce unknown and potentially unknowable risks, elevating the interactional difficulty for both patients and doctors in discussing (un)certainty.

Prognostic uncertainty and trial drugs

Biomedicine is rife with promissory notes (Fortun 2008) or the potential benefits of emerging technologies. Such promises are not foreign to experimental cancer medications (Morrissey 2019), with drugs situated as ‘silver bullets’ and miracle cures. However, in contrast to Fortun’s (2008) description of physicians, researchers and corporate actors emphasising the promises of trial drugs, physicians in our study struggle to assuage such optimism with realistic expectations. While above (Efficacy and Consequences) we detail how clinical trial interactions disrupt certainty in regard to when a patient might die, here we describe how trials question if a patient will succumb to their terminal cancer.

The potential of trial drugs is demonstrated in an interaction between Richard (a patient) and Dr. Souza. Richard has been informed that his cancer might be growing. Dr. Souza reports there is a 10% chance that this growth is ‘pseudo-progression’, wherein scans show a larger tumour, yet the cancer has not actually grown. There is also a 90% chance the progression is genuine, with Richard facing a difficult decision to either switch to another trial or transition to hospice care. Dr. Souza adds that the new trial will at best ‘extend’ or ‘stretch’ Richard’s lifespan, and the drug also carries a new set of side effects. After consulting with his wife, Richard decides to begin the new trial, “we think that you’re right and I think that I need something that’s stronger and I want something that goes after it. Kicks its butt to be totally honest.” Despite Dr. Souza’s emphasis that the trial drug is not curative, Richard suggests the drug will ‘kick [the] butt’ of his cancer. Accordingly, while Dr. Souza is carefully considering the efficacy of the drug, Richard perceives this new medication as potentially eliminating his terminal cancer.
In clinical trial interactions, physicians encountered difficulties managing such optimism. Yet patients face tough tasks, trying to make sense of difficult diagnosis and medications that may (or may not) provide tangible benefits. Nevertheless, these topics (diagnosis and treatment options) need to be communicated in realistic terms. Responding to Richard, Dr. Souza attempts to manage his expectations:

In general, the goal of this treatment would be to try to shrink the cancer in that area, to delay or slow down further progression, and hopefully, despite managing chemo side-effects, you could have an overall better quality of life - if the symptoms are manageable from the cancer and the side-effects are also manageable. Okay?

Dr. Souza downgrades Richard’s evaluation of the medication, noting it will only ‘shrink’, ‘delay’ or slow the progression of his cancer. That is, Richard might receive benefits but the drug is not curative. Despite the reframing, Richard responds, “I mean hopefully it’s a ticket to kill the cancer and have a miracle – but the side effects that I would most probably get, what would they be, besides hair loss?” Richard again emphasises the curative potential of the drug, while also minimising the side effects. As such, clinical interactions disrupt prognostic certainty, providing a ‘silver bullet’ or ‘lottery ticket’ that might eradicate terminal cancers.

Other participants were similarly optimistic vis-à-vis experimental drugs. For instance, Gary (a patient) asks his physician about the treatment potential of medical marijuana. Gary’s wife adds she thinks marijuana ‘sounds like a miracle’ because online sources report it is ‘curing’ cancers. Another patient asks his doctor if he has ‘heard of Watson’, IBM’s Question and Answer software that has been reported to outperform clinicians in diagnostic challenges, and whether that software might discover a trial drug to treat his cancer. In both circumstances, ‘outside the box’ thinking and experimental approaches are situated as disrupting patients’ terminal prognoses.

At times, doctors also emphasise the promising potential of trial drugs. For example, Dr. Blackwell tells Mary (a patient) of a drug that is showing ‘pretty impressive difference in what we call progression-free survival–meaning that we can’t even see the cancer’. Dr. Blackwell adds that the drug has not received FDA approval and is ‘not yet reporting cure rates’ but if the results continue, ‘we may just lay claim to curing more people’. Clearly, any drug with such results is appealing to someone living with terminal cancer. Unfortunately, as with many promissory notes in medicine, this drug failed to fulfil such lofty promises. The drug has since received FDA approval and while it does seem to extend life by several months, it falls short of delivering ‘progression-free survival’. Nonetheless, during these clinical interactions, this trial drug is the type of ‘miracle’ that Richard, Gary and other participants are pursuing, with descriptions of the drug disrupting the certainty of Mary and other participants’ cancers.

Discussion

Clinical trial medications are de facto uncertain. Indeed, part of what trials are designed to do is to better ascertain how these experimental compounds operate in the body (Corrigan 2002). In this article, we demonstrate how patient–doctor interactions regarding clinical trials introduce uncertainty in the context of terminal cancer. Study participants face a stark prognosis, they navigate extensive uncertainty with their health and future described in an ever-fluctuating combination of probabilities, in which ‘mights’ and ‘ifs’ are commonly associated with experimental medications. Such uncertainty is deeply implicated in the clinical encounters we describe, even though these encounters occur exceptionally close to the end of the life course.
and in the context of high prognostic certainty. As such, in contrast to macro theories of uncertainty and risk (Beck 1992, Giddens 1990), we argue that such uncertainty is produced and managed through interactions, with physicians both effectively communicating the risks (see Dr. Blackwell and Kristen’s interaction in Consequences for an example) or emphasising the curative potential (see Dr. Blackwell and Mary’s interaction in Prognosis for an example) of experimental medications.

In this article, we argued that patient–doctor interactions surrounding clinical trials introduce uncertainty into the context of a terminal cancer diagnosis. The study contributes to medical sociological work on death awareness (Glaser and Strauss 1965, Timmermans 1994). While Glaser and Strauss analyse information provision and Timmermans investigates emotions and patient perspectives, our study directs attention to interactions and the role of science and technology. Our study demonstrates how clinical trial interactions introduce temporal uncertainty into the context of open awareness, such that individuals with terminal conditions might be aware they are dying but nonetheless encounter considerable ambiguity in relation to when they might die. Patients are invited into clinical trials that might extend their lives by weeks, months, years or only result in distressing side effects and diminished quality-of-life. While Timmermans (1994) suggests patients can move between phases of open awareness, he does not explicate how this might occur. Here, we argue that clinical trial interactions provide a venue for both doctors and patients to move from active open awareness (i.e. explicit acceptance of a terminal prognosis) and uncertain open awareness (focus on possible positive outcomes), as trials interactions introduce the possibility of additional years of life and, in some instance, potential cancer remission. Revising both formulations of death awareness, we argue that death aware is not just about the information provided by physicians or the emotional experiences of patients but is also modulated by the implications of emerging science and technology that are manifest in patient–doctor interactions. We further suggest that death awareness is not just about if a patient will die but when they will die, with this latter question influenced by interactions surrounding experimental and potentially life-extending medications.

Physicians in our study frequently employed probabilistic language to discuss trial drugs, which supports prior findings regarding quantitative language, risk and uncertainty (Lautenbach et al. 2013, Lobb and Gaff 2010, Pilnick and Zayts 2014). Here, physicians’ quantitative and seemingly precise language describing clinical trial studies has the paradoxical effect of exacerbating uncertainty, as all outcomes are qualified by statistical language, unknown variables and mitigating factors. In this regard, clinical encounters can be ambiguous and uncertain, even when physicians rely on empirical findings consistent with an evidence-based medicine approach (see also Babrow et al. 1998, Gigerenzer and Edwards 2003, Segalowitz et al. 2016). Patient uncertainty is important as the framing of medical risk can impact how patients understand their condition and how they make treatment decisions (Littlejohn and Kimport 2017). For example, both Kristen and Richard’s perception of side effect risk was an important factor in whether they would enter a clinical trial. As participants routinely worried about the quality and quantity of their remaining life, the uncertainty of clinical trials had implications for both themselves and their families.

Our findings demonstrate the interactional difficulty in explaining the uncertainties and risks inherent in clinical trials (see Dr. Souza and Richard’s interaction in Prognosis for an example). Addressing such uncertainty is an essential part of patient-centred care (e.g. Epstein and Street 2007) and is a well-established challenge in patient–doctor interactions (Epstein and Street 2007, Jones 2013, Pilnick and Zayts 2014, Pryer and Hewitt 2010). Indeed, even when physicians combine technical information with commonly used language, doctors cannot predict how a specific patient will react to an experimental drug. Based on our findings, we suggest that acknowledging the limits of medical knowledge can expand the co-constructed
understanding of uncertainty and risk (see Dr. Blackwell and Kristen’s interaction in Consequences for an example). Here, future studies are necessary, particular those that analyse if directly mentioning interactional difficulties helps patients to prepare for the potential uncertainties in relation to clinical trials.

The interactional components relevant to uncertainty and clinical trials that we detail are also salient for physicians’ practices. Based on our findings, physicians might discuss the temporal features of uncertainty, noting how the benefits and risks of trial medications unfold over time and intersect with cancer growth or shrinkage. Similarly, while probabilistic language might accurately reflect clinical trial data, the current study suggesting probabilistic language also complicates patients’ perceptions of prognostic certainty. Understanding the components of clinical trial interactions might also help identify avenues for discussing other options (e.g. palliative care), which is especially salient for patients who are enrolling in trials because there are no other viable anti-cancer treatments. By using examples of interactional misunderstandings or challenges, physicians might prepare all conversational parties for the difficulties associated with clinical trials.

Future researchers might employ other qualitative methods (e.g. conversation analysis in-depth interviews). In contrast to our study, conversation analysis might identify the micro-features of interactions characterised by uncertainty, or detail language that facilitates the joint management of uncertainty to strengthen patient–doctor interactions. Likewise, in-depth interviews might better reflect the feelings, thoughts and experiences of patients that surround clinical trial interactions. By employing a micro-level approach and interactionist frame, we provide one demonstration of the analytic potential of such studies in relation to health, medicine and uncertainty.

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Conflict of interest

We have no conflicting interests to declare.

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