Terminally-Ill Jewish Patients and Access to the FDA's Expanded Access Program: Medical and Religious Decision Making During End-Stage Disease

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Abstract

Individuals of the Ultra-Orthodox Jewish (UOJ) faith who are diagnosed with a terminal illness are not exempt from the obligations of their religion. In this thesis, I examine how terminally-ill UOJ individuals, with input from authoritative rabbis, perform their religious duty to maximize lifespan by enrolling in the FDA's Expanded Access Program (EAP). The EAP allows terminally-ill patients to gain access to experimental medications and avoid the uncertainty inherent in clinical trials. The thesis contains my review of Talmudic tractates, rabbinic rulings, and codes of Jewish law that establish the origins of the precedent to protect health and by extension increase lifespan. Following this line of inquiry, I explore differences between religiously-informed and medically-informed definitions of terminal illness and medical futility, thus exemplifying how miscommunication between UOJ patients, rabbis, and physicians leads to the pursuit of medical care some deem extreme or not aligned with the standard of care.

Shifting away from religious topics, I investigate the process by which applications to the EAP are evaluated, demonstrating that a lack of standardization and transparency results in an inequitable allocation of experimental medications. My analysis of solutions proposed to address the need for consistency and openness in the EAP review process demonstrates that the required inclusion of patient narratives remains unsatisfactory, especially when reviewing applications with unique religious or social dimensions. I argue that unique social or religious concerns must be reviewed by appropriate experts instead of reviewers who lack an understanding of important non-clinical factors. Concerning individuals of the UOJ faith, a rabbi or scholar of, *halakha*, Jewish law, is needed to identify and analyze religiously informed aspects of a patient narrative.

Returning to Jewish law, my analysis of rabbinic writings on medical uncertainty establishes why the EAP is considered a superior option to clinical trial participation. I then analyze data from palliative care research to show this form of medical care also satisfies rabbinic positions on risk mitigation and end of life care. By recasting palliative care as a series of interventions that can improve the quality and quantity of life, I confirm the halakhic acceptability of this model of care. This thesis concludes with the introduction of a framework that is designed to improve the process by which patient narratives that contain religious motives are reviewed. In closing, my exploration of Jewish law, rabbinic writings, and clinical research demonstrate that UOJ applications to the EAP must be both halakhically and medically appropriate.

Résumé

Les individus de foi juive ultra-orthodoxe (JUO) diagnostiqués avec une maladie terminale ne sont pas exemptés de leurs obligations religieuses. Dans ce mémoire, j'examine comment les personnes JUO en phase terminale accomplissent leur devoir religieux de maximiser leur durée de vie en s'inscrivant au programme d'accès élargi (PAE) de la FDA, avec l'aide d'autorités rabbiniques. Le PAE permet aux patients en phase terminale d'avoir accès à des médicaments expérimentaux et d'éviter l'incertitude relative aux essais cliniques. Ce mémoire contient mon examen des chapitres talmudiques, des décisions rabbiniques et des codes de la Loi juive établissant les origines du précédent de protection de la santé et, par le fait même, de prolongement de la durée de vie. En suivant cette piste d'analyse, j'explore les différences entre les définitions religieuses et médicales de la maladie terminale et de la futilité médicale, illustrant en quoi une mauvaise communication entre les patients JUO, les rabbins et les médecins conduit à la poursuite de soins médicaux considérés extrêmes ou non conformes à la norme de soins.

Délaissant les sujets religieux, j'étudie le processus d'évaluation des demandes adressées au PAE, démontrant qu'un manque de normalisation et de transparence entraîne une répartition inéquitable des médicaments expérimentaux. Mon analyse des solutions proposées pour répondre au besoin de cohérence et d'ouverture dans le processus d'évaluation du PAE démontre que l'inclusion obligatoire des récits des patients demeure insuffisante, plus particulièrement lors de l'examen de demandes ayant des dimensions religieuses ou sociales uniques. Je soutiens que les préoccupations sociales ou religieuses uniques doivent être examinées par des experts compétents plutôt que par des examinateurs qui ne comprennent pas les facteurs non cliniques importants. En ce qui concerne les personnes JUO, un rabbin ou un spécialiste de la *Halakha* est nécessaire pour identifier et analyser les aspects religieux du récit d'un patient.

Revenant à la Loi juive, mon analyse des écrits rabbiniques sur l'incertitude médicale établit pourquoi le PAE est considéré comme une option supérieure à la participation à un essai clinique. J'analyse ensuite les données de la recherche en soins palliatifs pour montrer que cette forme de soins médicaux répond également aux positions rabbiniques quant à l'atténuation des risques et aux soins de fin de vie. En repensant les soins palliatifs comme une série d'interventions pouvant améliorer la qualité et la quantité de vie, je confirme l'acceptabilité halakhique de ce modèle de soins. Ce mémoire se termine par l'introduction d'un cadre conçu pour améliorer le processus par lequel les récits des patients qui contiennent des motifs religieux sont examinés. Pour conclure, mon exploration de la Loi juive, des écrits rabbiniques et de la recherche clinique démontre que les demandes JUO au PAE doivent être à la fois religieusement et médicalement appropriées.

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I would be remiss if I did not thank the McGill University Biomedical Ethics Unit and the generous funding provided by the I.M. Rabinowitch Fellowship. From my first day of classes, I felt welcome and respected by peers and faculty members.

Lastly, I must thank my family. Without question, the support I have received from my father Lawrence, and my mother Jodi has shaped me into the man I am today.

After thanking those who helped me reach this milestone I would like to acknowledge the lives lost and sacrifices made during this pandemic. The Talmud states “The best physicians are destined for hell” over the past year front-line and health care workers have willingly exposed themselves to dangerous situations and experienced the hell of this pandemic. Although I cannot thank each one individually, their willingness to face the challenges of this pandemic hand-in-hand with members of their community is a testament to human endurance and empathy.

Humbly,

Joshua Moise-Silverman

Contribution of Authors

Joshua Moise-Silverman is the sole academic contributor to this thesis. All analyses, assertions, and conclusions - both correct and objectionable - are his, and his alone. Joshua identified and analyzed relevant religious, medical, and bioethics texts under the guidance of Dr. Jennifer Fishman, Associate Professor in the Biomedical Ethics Unit, and the Department of the Social Studies of Medicine, McGill University. He completed all original analyses and lines of inquiry found in each chapter without outside assistance. Dr. Fishman provided editorial, methodological, and technical advice for each chapter. No funding was provided for this thesis. Relevant texts were accessed via the McGill University library; when necessary additional resources were borrowed from academics, Rabbis, yeshivas, other universities, or purchased with personal funds.

Glossary of Terms

Ashkenazi Jew:

One of two major ancestral groups of Jewish individuals. Before a series of migrations Ashkenazi Jews lived in Central and Eastern Europe. Ashkenazi Jews comprise the majority of North American Jews.

Babylonian Talmud:

A compilation of legal opinions, dialog between Jewish scholars, and stories about Rabbinic figures who lived between 0-500 CE. In addition to purely theological topics the Talmud deals with civil, criminal, and matrimonial law.

Chayei sha'a or Treifah:

Chayei sha'a/Treifah refers to a terminally ill individual who is thought to have less than a year of remaining lifespan.

Halakha

Jewish law derived from the Oral Torah and Written Torah.

Mishneh Torah

A codification of Jewish law authored by Maimonides between the 11th and 12th centuries of the common era.

Oral Torah

The entirety of Jewish law not recorded in the Written Torah. The teachings of the Oral Torah can be found in the Talmud. Members of the Ultra-Orthodox Jewish community strictly adhere to the laws of the Oral Torah.

Posek

Scholars who interpret and provide rulings on the positions of Jewish law.

Psak

A ruling on the position of Jewish law, as issued by a Posek.

Safek Goses

Within Jewish law a goses is a person who is expected to die within 72 hours.

Shulchan Aruch

Authored by Rabbi Joseph Caro in 1560 (C.E), this publication is considered to be an authoritative collection of Jewish law.

Tractate

A section or chapter of the Talmud.

Ultra-Orthodox Judaism

The lifestyle and religious practice of Ultra-Orthodox Jewish individuals is characterized by strict adherence to Jewish law and avoidance of secular values and practices.

Written Torah

The five books of the Hebrew Bible.

Chapter One:
Introduction

A History of Extreme Care

The Jewish faith is a living tradition that coevolves with social, scientific, and technological advances. This parallel relationship is observable in many areas of Jewish life but is salient during times of illness. As medical discoveries related to life-limiting illnesses continue, Ultra-Orthodox Jews (UOJ) are frequently forced to reconsider what modes of medical care should or should not be delivered to the terminally ill. For some, no level of care is too high.

There is a well-documented history of terminally-ill Ultra-Orthodox Jews electing to pursue medical care some physicians deem extreme. The treatment of Rabbi Menachem Mendel Schneerson, known as the Rebbe, illustrates the UOJ emphasis to extend life even for those in extremis. After the Rebbe's heart attack a fully functional cardiac ICU was built in their house despite his doctor's instance that a hospital would provide better care ('An Interview with the Rebbe's Doctor - Dr. Ira Weiss' 2020). Furthermore, the delivery of medical care was dictated by Rabbi Schneerson's rabbinical colleagues not his physicians - who were flown in from around the world. Equally illustrative examples of rabbis determining a course of medical treatment can be seen in the scholarship of Rabbi Akiva Tatz. Rabbi Tatz's case studies reveal that patients of the Ultra-Orthodox Jewish faith often follow the advice of their rabbis and make medical decisions in opposition to their doctor's advice (Tatz 2010a, sec. Clinical Cases). Dr. Fred Rosner's authoritative publication *Modern Medicine and Jewish Ethics* also examines episodes in which terminally-ill UOJ patients or their rabbis request doctors take heroic measures to treat an ultimately lethal condition (Rosner 1972, sec. Heroic Measures).

A final contemporary example of religious authorities overriding medical recommendations was provided during a conversation I had with a rabbi who wishes to remain anonymous. This rabbi, who is internationally held in high regard, discussed the case of a congregant who was diagnosed with terminal cancer. The patient had a tumor that was creating a fistula between their bladder and bowel. Surgeons claimed the complex procedure needed to repair the fistula would not improve the patient's quality of life and was unlikely to increase their quantity of life. After receiving the recommendation to avoid the surgery, this patient consulted the rabbi, who supported the patient's decision to undergo the operation deeming it religiously permissible. During a discussion with me, the rabbi rationalized his advice by stating the procedure could potentially improve lifespan; however, they also revealed this patient underwent a successful operation and died soon after. This episode, and many others, illustrate a tension between secular and religious approaches to the management of terminal conditions.

Recently, a small number of reports authored by Rabbi Akiva Tatz, Joan Bayes, and others have indicated this friction has spilled over from the clinic into clinical trials and the FDA's Expanded Access Program (EAP). The EAP provides experimental medication outside the context of a clinical trial. This thesis represents a four-part examination of both theoretical and applied issues related to members of the Ultra-Orthodox Jewish community attempting to bypass the uncertainty of clinical trials by enrolling in the EAP.

First, I provide an analysis of Jewish law and rabbinic writings and elucidate why UOJ individuals are obligated to protect their health and decrease medical-related uncertainty, specifically uncertainty related to outcome. Following this analysis, I introduce the EAP application review process and examine challenges related to the equitable review of applications. Additionally, my exploration of rabbinic writings on the minimization of medical risk illustrates why the EAP is an attractive treatment option for UOJ patients. Finally, by comparing medications provided via the EAP and the benefits of palliative care I demonstrate that terminally ill individuals of the UOJ faith can satisfy Jewish law by receiving palliative care instead of experimental medications.

Chapter Summary

Chapter Three: What are the Ultra-Orthodox Jewish Obligations to Maintain Health?

Before exploring issues with the Expanded Access Program, readers of this thesis must familiarize themselves with the approaches of the Jewish religion to end of life medical care. To this end, Chapter Three contains an examination of religious texts which establish the precedent to maintain one's health and extend one's lifespan. Analysis of Talmudic tractates, rabbinic legal rulings known as psaks, and writings by prominent rabbis highlights why UOJ individuals diagnosed with a terminal condition claim they are obliged to pursue aggressive treatment options.

The majority of the religious texts cited and rabbis referenced in this thesis originate from Ashkenazi sources. North American Jewry is dominated by Ashkenazim, members of this community are more likely to publish their rulings in English, thus increasing their audience and influence within Ultra-Orthodox and greater Jewish communities. Despite a reliance on Ashkenazi texts and rabbis, the foundational texts explored in this thesis, specifically the Babylonian Talmud and Maimonides Mishneh Torah, are studied by members of Sephardic, Mizrahi, Romanoite, and other Jewish communities. The chief focus of this thesis is the Ashkenazi community, but the universal use of the Talmud in the Jewish faith indicates the majority of the positions examined in Chapter Three are present in various Jewish communities.

The Talmud is a collection of religious laws and theology. Through the study of biblical texts, case studies, rabbinic writings, aphorisms, and thought experiments this collection of teachings illustrates how Judaism directs a person to act in the world (Telushkin 1991). The

Babylonian Talmud was first complied between the Third and Sixth centuries of the common era; due to the age of the Talmud many contemporary issues within Jewish society are not addressed. A lack of Talmudic guidance on the challenges of modern life resulted in the training of specialized rabbis, referred to as poseks. By studying Talmudic precedent, poseks provide authoritative rulings - psaks - on current issues for their particular community (Breitowitz 1996). Psaks while authoritative are not universal as different Jewish sects have their own poseks and by extension unique rulings on various issues. The multiplicity of rulings indicates there is no 'standard' or 'correct' interpretation of Jewish law, otherwise known as halakha. While certain aspects of the religion are agreed upon others are hotly debated. Medical halakha which addresses the care of those diagnosed with a terminal illness is an incredibly contentious topic.

After completing an examination of Talmudic writings and associated psaks, Chapter Three closes with a comparison of UOJ and secular medical concepts, such as risk, terminal illness, and futility. The use and comprehension of the aforementioned terms vary between secular and religious individuals. Physicians and UOJ patients often employ different definitions, thus establishing the precedent of miscommunication, misunderstanding, and misalignment of medical objectives and desired outcomes. The end of this chapter illustrates why religious teachings and miscommunication between the patient, physician, and rabbi encourages UOJ patients diagnosed with a terminal condition to apply to the FDA's Expanded Access Program.

Chapter Four: The FDA's Expanded Access Program

The FDA's Expanded Access Program is unique as it facilitates access to experimental medications outside the context of clinical trials (Holbein et al. 2015). To understand current issues with this program Chapter Four begins with a summary of the EAP's history. A close review of the EAP's regulatory history reveals why interest in this program has grown over the years and how federal regulations have obfuscated the inner workings of the application review process.

Analysis of EAP application review procedures reveals this program is markedly different from other federal programs. Pharmaceutical companies, the FDA, and IRBs evaluate patient materials and determine approval. Many pharmaceutical companies and IRBs do not publish internal EAP policies or rosters of professionals who evaluate these applications, despite laws claiming they must. This lack of transparency is a known flaw that has become increasingly worrisome. The FDA is the only organization that consistently publishes data: over 95% of applications that are transmitted to the FDA from pharmaceutical companies are approved (Commissioner 2020). Some scholars argue that this approval rate is alarmingly high and indicates a failure of pharmaceutical companies to self-regulate.

A small number of pharmaceutical companies and research centers have published peer-reviewed articles on their internal EAP review policies and patient outcomes (A. L. Caplan et al. 2018; Chapman, Shearston, et al. 2019; Lawrence 2019). These publications often focus on a demarcated set of topics such as how to best report and respond to adverse drug reactions or how to fund these programs.

Patient narratives, while incredibly important, are often not included in EAP applications or they are overlooked or ignored during the application review process. These narratives provide vital information to those entrusted with the duty to approve or deny an application. To illustrate the importance of authentic patient narratives, Chapter Four includes an analysis of publications authored by members of the Johnson and Johnson Pharmaceuticals EAP review committee as well as clinical vignettes (A. L. Caplan et al. 2018). These two lines of inquiry illustrate how the absence of a narrative hinders a reviewer's ability to determine which terminally-ill individuals should receive access to the limited quantities of an experimental medication and which should not.

Narratives allow those who review EAP applications to consider important clinical and non-clinical information. The author asserts that these motives can only be assessed appropriately when the ‘correct’ experts are employed. Connecting this issue back to that of transparency Chapter Four concludes with a question, are members of EAP review panels able to appropriately assess narratives that reveal unique social or religious motives, such as those informed by the Ultra-Orthodox-Jewish faith?

Chapter Five: Rabbinic Arguments for Enrollment in the Expanded Access Program

Both the EAP and clinical trials provide access to experimental medications, but why do Ultra-Orthodox Jewish patients appear to favor participation in the EAP? To answer this question Chapter Five begins with an exploration of UOJ individuals’ attitudes towards risk and clinical trial participation. There are multiple reasons why a UOJ individual may elect to avoid a clinical trial; some of these reasons overlap with those described in secular research efforts, others appear to be uniquely religious in origin (Veatch 2000, sec. An Obligation to Heal in the Judaic Tradition; Carmell and Domb 2000, sec. Medical Experimentation on Humans). Analysis of the work of Joan Box Bayes, a researcher who explores Jewish outlooks on clinical trial participation, provides insights on the religious justifications used to avoid or enroll in a clinical trial. Combining the work of Bayes with the work of Rabbi Akiva Tatz provides additional data from which Jewish religious positions on clinical-trial participation are scrutinized. This line of inquiry is anchored via a comparison of possible religious rationalizations to enroll in the EAP with other Jewish laws that permit the breaking of halakhic precedent to save a life.

In addition to purely religious motives, medical decisions made at the end of life often involve the completion of a risk-benefit analysis. The risks and benefits considered by a UOJ patient diagnosed with a terminal illness differ greatly from those made by individuals with secular belief systems (Breuer, Rosner, and Glatt 2011). Studying the psaks of three medical halakhists who perform risk-benefit analyses - Rabbis Steinberg, Feinstein, and Waldenberg - elucidates how an individual diagnosed with a terminal illness rationalizes treatment decisions or decides to enroll in the EAP.

The remainder of Chapter Five is devoted to uncertainty, specifically defining what uncertainty means within a medical and religious context. This exploration reveals how UOJ individuals respond to the ambiguity of outcome and answer the question “Is there a religious obligation to minimize uncertainty?” Ultimately this analysis reveals why UOJ individuals diagnosed with a terminal illness attempt to minimize treatment-related risk and uncertainty by enrolling in the EAP.

Chapter Six: Halkahically Permissible Alternatives to EAP Participation

Chapter Six begins with a continuation of the topics introduced in Chapter Five. Instead of using Talmudic and halakhic precedent to explore why UOJ individuals with a terminal illness attempt to enroll in the EAP, this chapter examines how the same texts and rabbinic writings can be interpreted to support treatment alternatives, specifically palliative care. Historically, individuals of the Ultra-Orthodox Jewish faith have a fraught relationship with palliative medicine (Barilan 2003). To many enrolling in palliative care appears to be antithetical to the teachings of the Jewish faith, it is an admission of failure. Despite this view, it appears that palliative care satisfies many of the criteria considered when one performs a halakhically informed risk-benefit analysis. By once more examining the work of Rabbis Steinberg, Feinstein, and Waldenberg, arguments advanced in Chapter Six illustrate that palliative care is not only halakhically acceptable, it may be preferred to enrollment in a clinical trial or the EAP.

In recent years palliative care research has undergone a quantitative shift, the move towards data-driven end of life care has provided concrete evidence for phenomena that were previously anecdotal (Kelley and Meier 2010). Of note, several recent research efforts have shown that in certain scenarios palliative care can increase both quality and quantity of life as compared to standard of care (Bakitas et al. 2015; Bauman and Temel 2014; Kavalieratos et al. 2016). Utilizing data from palliative care research, I demonstrate that palliative care satisfies Jewish law. Furthermore, analysis of data from palliative care studies and the EAP confirms that palliative care minimizes uncertainty of poor outcomes, unlike participation in the EAP which does not. By establishing the effectiveness and halakhic acceptability of palliative care, this author asserts that patient education and dialogue between rabbis and physicians is needed to illustrate the various treatment options a terminally ill UOJ patient can pursue.

Discussion and Concluding Remarks

This thesis concludes with a pair of open-ended questions. 1) Do the issues explored herein represent a sentinel case? 2) Can EAP reviewers appropriately assess any patient narrative that references religious or social values? While it is not my goal to make substantive recommendations, a brief introduction to the work of James Buryska and his framework for evaluating the social and religious significance of patient requests illustrates that it is possible to fairly evaluate requests which originate from a religious claim (Buryska 2001). Ultimately religiously informed demands are not that different from those made by secular persons, both require careful consideration. Utilizing appropriate expertise, educating patients, and considering valid alternatives will ensure those of the UOJ faith, and all members of terminal illness communities trust the process by which applications to the EAP are reviewed and experimental medications are allocated.

Chapter Two:
Methodology

The research performed in this thesis is interdisciplinary. I performed a narrative review of relevant topics and employed both qualitative and quantitative techniques from the fields of Jewish legal theory, religious studies, bioethics, and medicine to complete the analyses found here-in.

Chapter Three

The arguments presented in Chapter Three are informed by my review of Jewish legal texts, Talmudic tractates, rabbinic writings, and scientific literature. To summarize the Ultra-Orthodox Jewish religions approach to the maintenance of health and end of life medical care, I identified and reviewed relevant texts. Talmudic tractates were identified by searching an online Talmud database with the following search terms: Health, End of Life, Goses, Risky Medical Treatment, Safek, Safek Goses, and Terefah. I analyzed the contents of Talmudic texts via a combination of exegetic analysis and the Britzker method. Both of these approaches are well defined elsewhere and will not be described for the sake of brevity. In addition to analysis of core texts, the contents of accompanying Barrita, Gemara, and when appropriate contemporary scholarship were reviewed via the aforementioned methods.

After completing my analysis of core Talmudic tractates, I performed a search for psaks and responsum that referenced the previously examined sections of the Talmud. Psaks on terminal illness and the importance of maintaining one's health were sourced from collections of responsum (published in English) by Rabbis Aurbach, Feinstein, Jokowitz, Steinberg, Tatz, Tendler, Waldenburg, and their posekim (students). I relied upon the work of these aforementioned Rabbis as they are considered authoritative within the field of medical halakha.

Books on Jewish medical ethics which were authored by Rabbis Feinstein, Tendler, and Tatz were used as reference texts as these publications are simplified to reach secular audiences.

To identify religiously informed definitions of terminal illness I searched the following phrases in the Talmud, Schulan Aruch, and Mishneh Torah; Terminal Illness, Terminal, Terefah, Safek, and Safek Goses. I then used my findings to perform a second search in the responsum of the previously mentioned Rabbis

When examining secular definitions of terminal illness and medical futility relevant publications were searched via PubMed. The following search terms were used; End-Stage Disease, Futile, Medical Futility, Medical Irreversibility, Terminal Illness, and Terminally Ill. Definitions provided by systematic or meta-reviews were used whenever possible. The same search terms were used when identifying definitions provided by the U.S. Code of Federal Regulations.

Chapter Four:

The content of Chapter Four includes a synopsis of the legislative and regulatory history of the FDA’s Expanded Access Program. This chapter also contains a critical analysis of issues with the EAP application review process. Previous versions of EAP legislation were identified by searching ‘21 CFR 312 Subpart I’ on the United States Government’s electronic code of federal regulations website.

A PubMed search using the keywords: Compassionate Use Program, EA, EAP, Expanded Access, Expanded Use, Expanded Access Program, Parallel Access Program, Right-to-Try Act, Treatment IND, and Treatment Investigational New Drug, was used to identify scholarship that examines the EAP’s legislative history. The same search terms were used to identify peer-reviewed articles that examine issues with current application review procedures

Published pharmaceutical company EAP policies were accessed via the Regan-Udall Foundations Expanded Access Navigator. Publicly available IRB policies were identified by reading peer-reviewed research on the topic. The FDA’s EAP review policies were accessed via public statements issued by CBER and CDER, in addition to peer-reviewed publications authored by employees of the FDA. Data on EAP application approval rates were provided in the FDA Program Commissioner's yearly report.

EAP safety data, which is not published on clinicaltrials.gov was collected from several single-site retrospective studies. These studies were identified via PubMed searches with the following keywords; CBER, CDER, CUPA, EAP, Expanded Access Program, EA Policies, Expanded Access Policies, EA IRB, Expanded Access IRB, EA Patient Safety, EAP Pharmaceutical(s), EA ADR, Expanded Access Program Adverse Drug Reaction, IND Adverse Drug Reaction(s), Single-Patient IND, and Single-Patient IND Outcomes.

Finally, I decided to utilize clinical vignettes with the goal of highlighting lesser-known issues with the EAP application review process. The vignettes were analyzed via an approach grounded in narrative ethics. These vignettes are purely hypothetical, any similarity to real-world cases is incidental.

Chapter Five:

Chapters Three and Four introduce the reader to various concepts within the Jewish Religion and provide a brief overview of the EAP. The majority of the qualitative analysis found in this thesis is found in Chapters Five and Six. Chapter Five asks and answers the following question; why does Jewish law appear to support participation in the EAP over participation in clinical trials? To answer this question, I examined the UOJ approach to medical risk-taking.

Psaks and rabbinic writings on the uncertainty of clinical trials were identified via searching the Sefaria database, the following keywords were used: Clinical Trial, Experimental Medicine, Medical Ethics, Medical Risk, Medical Trial, and Medical Uncertainty. When possible psaks which advanced quantitative cut-offs for excessive risk - i.e. a 35% chance of an ADR is unacceptable - were used instead of psaks which did not provide numerical values.

In addition to rabbinic sources, academic research on Jewish attitudes towards clinical trial participation was accessed via PubMed, the following keywords were used when performing searches: Jewish Participation Clinical Trials, Orthodox Judaism Experimental Medicine, Orthodox Judaism Medical Risk, Ultra-Orthodox Judaism Clinical Trials.

Data gathered from the aforementioned literature searches was compared to data on the risks of participation in the EAP. By identifying the risks of participation in the EAP, I was able to compare this risk burden to statistical cutoffs advanced by rabbinic authorities. After demonstrating that INDs provided via the EAP do not exceed religiously informed risk thresholds, I performed an exegetic analysis of psaks on medical risk-taking that were authored by Rabbis Feinstein, Steinberg, and Waldenberg. Thus, establishing why clinical trial participation is deemed inferior to participation in the EAP.

Finally, data from the two aforementioned lines of inquiry were integrated into my examination of the UOJ religion's approach to medical uncertainty. My exegetic analysis of psaks on medical uncertainty, identified via the following search terms: Clinical Trial(s), Experimental Medicine, Medical Ethics, Medical Risk, Medical Trial, and Medical Uncertainty, proves that the onus to decrease medical risk and uncertainty encourage patients of UOJ faith to enroll in the EAP.

Chapter Six:

Whereas the lines of inquiry present in Chapter Five establish why EAP participation is preferred to clinical trial participation, arguments advanced in Chapter Six assert that palliative care represents a medically and religiously viable alternative to enrollment in the EAP. The claims made in this chapter are informed by quantitative and qualitative data provided by studies on the effectiveness of palliative care. These studies were identified by using the following search terms in PubMed: Integration of Palliative Care, Palliative Care Clinical Trials, Palliative Care Life Expectancy, Palliative Care Outcomes, Palliative Care Quality-of-Life, Palliative Care Quantity-of-Life.

Quantitative data from the previously identified palliative care research was compared to data provided from peer-reviewed single-site studies that examine the safety of INDs provided via the EAP. A comparison of data from palliative care research to available EAP data shows that patient’s enrolled in palliative care were more likely to experience improved quality and quantity of life.

After using quantitative methods to establish the efficacy of palliative care, the halakhic acceptability of participation in palliative care programs was established by applying data from these studies to the psaks of Rabbis, Feinstein, Waldenburg, and Tendler. Analyses of these psaks, which are informed by contemporary data on palliative care, illustrate that palliative care's ability to minimize uncertainty and maximize lifespan makes the receipt of palliative medications and interventions an acceptable alternative to enrollment in the EAP.

Chapter Three:

What are the Ultra-Orthodox Jewish Obligations to Maintain Health?

Receiving the diagnosis of a terminal illness or condition is a life-altering event. Recipients of this information must navigate medical concerns and familial, social, and financial obligations - all while coping with the realities of a life-limiting disease (Woo, Maytal, and Stern 2006). When investigating the behavior of terminally ill Ultra-Orthodox Jews a common observation is the religion's emphasis on the maintenance of health (Barilan 2003). Practically, religious obligations to maintain health complicates the development and delivery of an equitable treatment plan; under ideal circumstances, any medical decision is realistic and sensitive to religious beliefs. In reality, the nuances of the Jewish faith and halakha related to end of life care represent a set of non-clinical factors that healthcare professionals must navigate when delivering a level of care commensurate with their patients' diagnosis and religious obligations.

Clear and open dialogue between a UOJ patient and their physician identifies many salient issues, but miscommunication continues to be problematic. Communication problems lead to a misunderstanding of diagnosis and prognosis (Bernacki, Block, and American College of Physicians High-Value Care Task Force 2014). These points of confusion are further exacerbated when UOJ patients consult a third party to assist with the development and selection of a treatment plan; the addition of rabbinic guidance eases a patient’s decision-making but also generates new obstacles (Breuer, Rosner, and Glatt 2011). Physicians utilize language and heuristics that are unique to the field of medicine. Similarly, rabbis employ language and frameworks unique to the Jewish religion. Patients and their families are stuck firmly in the middle of this communication network. As such, when patients speak to rabbis or physicians they use the same phrases and language in both settings, but the terms used have different interpretations depending on the conversation partner. One can observe the use of differing -

incompatible language - when exploring the medical and Orthodox Jewish definitions of terminal illness and medical futility. Employing different definitions creates a breakdown in communication which influences a patient’s decision-making process and ultimately patient outcomes.

To understand how decisions surrounding terminal illness can be influenced by misalignment and miscommunication of therapeutic goals, this chapter examines the obligations of Ultra-Orthodox Jews to maintain their health. Following the inspection of relevant religious texts, differences in the religious and medical definitions of terminal illness and medical futility are explored. Thirdly, the role of rabbis in the medical decision-making process is analyzed. Investigation of the aforementioned topics elucidates how breakdowns of patient, physician, and rabbi communication encourage some patients of UOJ faith to pursue ‘extreme’ medical care outside the context of normal medical care or a clinical trial.

The Jewish Faith and the Obligation to Save a Life

Several foundational Jewish texts and legal codes assert that an individual’s body is not their property, rather it is G-d’s. Upon birth, a spirit enters the body, the spirit which inhabits the gifted body must take care of it until death, at which point the body is returned to G-d (Schenker 2008). This belief has led to a series of rabbinic assertions which encourage Jewish individuals to take actions that protect G-d’s property and by extension their health.

Rabbi Moshe Tendler and Dr. Fred Rosner authored a series of papers that examine both the obligations of a Jew to protect their health and the theorized upper limit of this responsibility (Tendler and Rosner 1993). These analyses rely upon a series of Talmudic tractates and exegetic analysis of the Mishneh Torah. The core tractates explored are Sanhedrin 37a and 84a. Sanhedrin 37a states “ to save one life is tantamount to saving a whole world”, thus indicating human life is infinitely valuable (‘Sanhedrin 37a’ n.d.). The emphasis on the value of human life is of such importance that all but the three major sins – idolatry, adultery, and zoophilia - can be transgressed to save a life. Yoma85b further illustrates the value of human life, this section of the Talmud asserts that one can disregard the observation of Shabbat to save a life (‘Yoma 85b’ n.d.). Observing Shabbat is the greatest non-Noahide law, as such rabbis have asserted that all but the three aforementioned laws can be broken to save a life.

The upper limit of one's duty to maintain their health is explored in Sanhedrin 84a, this section of the Talmud introduces a utilitarian logic that elucidates when and why someone must be left to die (‘Sanhedrin 84a’ n.d.). Maimonides, a prominent rabbi, and physician who lived during the 12th century, interprets the language of Sanhedrin 84a, his reading states that if attempting to save a life puts the potential rescuer in mortal danger, they must allow the person to die (Bos 1994). There is no net gain if one person lives and the other dies.

Maimonides also advances risk mitigation strategies discussed in the Torah. Parashat Ki Tietzi in Deuteronomy states “When you build a new house, you shall make a parapet for your roof, so that you do not bring bloodguilt on your house if anyone should fall from it” (‘Parashat Ki Teitzei’ n.d.). Maimonides analysis of the aforementioned Parashat states

> “Both the roof and any other object of potential danger, by which it is likely that a person could be fatally injured, require that the owner take action… just as the Torah commands us to make a fence on the roof… and so, too, regarding any obstacle which could cause mortal danger, one, not just the owner, has a positive commandment to remove it… if one does not remove it but leaves those obstacles constituting potential danger, one transgresses a positive commandment and negates a negative commandment ‘Thou shall not spill blood’(Bos 1994).

Maimonides's interpretation of the construction of a literal handrail is often invoked when rationalizing actions taken to protect one's health against potential danger. Rabbinic authorities reference the handrail metaphor and Maimonides's writings on the subject to support the assertation that Jews must pursue any medical treatment which may improve their health, this belief extends to the treatment of the terminally ill (Rosner 1972, sec. The End of Life; Talmudic Sources). For relatively healthy Orthodox Jews preserving health includes regular physician visits, taking medications, and abstaining from activities known to carry a high risk of injury or death (Feinstein and Tendler 1996, sec. Quality and Sanctity of Life, a Torah View). These actions fall under the prudent man standard; any action a prudent man would complete to maintain their health must be done. When religious laws and rules surrounding the maintenance of one's health are applied to the terminally ill a similar set of actions are endorsed. Ultra-Orthodox Jewish patients are expected to pursue any treatment or therapy which may eliminate disease or maintain/extend life (Tendler and Rosner 1993, sec. Quality and Sanctity of Life, a Torah View; Tatz 2010a, sec. Limits of Risk). Despite the emphasis on the maintenance of health, there is an upper limit to the actions a terminally ill individual must take, but the threshold of these obligations is nebulous.

Jewish Faith and Maximization of Lifespan

The Jewish faith emphasizes the importance of taking action to maintain one's health, however, little attention had been paid to the challenges associated with increasing one's lifespan. Specifically, are there situations where the Jewish religion permits death instead of encouraging life? Examination of two Talmudic tractates illustrates that there are scenarios where death is not only accepted but encouraged.

Concerning intractable physical pain, the tractate Avoda Zara 18a, which describes the execution of Rabbi Hanina Ben Teradon, indicates death is preferred to prolonged suffering. Rabbi Hanina was sentenced to death by the Romans, this execution was to occur by wrapping the Rabbi in a Torah, then lighting it on fire. The Roman executioner placed wet wool between the Rabbi and the Torah to prolong his suffering. After being set on fire it is reported that Rabbi Hanina held his breath to prevent dying from smoke inhalation, the Talmud also states that the Rabbi's executioner, in a moment of anger, removed the wool and increased the flames, thus hastening Hanina's death. Scholars who have analyzed this tractate often discuss how two of this story's features indicate that those of Jewish faith need not take every possible action to delay death ('Avodah Zarah 18a' n.d.; 'Daf Shevui to Avodah Zarah 18a' n.d.).

1) Rabbi Hanina allows the wet wool to be removed from his body. The removal of an impediment to death indicates a quick death was the ideal outcome.
2) Rabbi Hanina allows the fire's strength to be increased but continues to hold his breath, thus not directly hastening his death and avoiding an action that can be considered suicidal in nature.

The story of Rabbi Hanina indicates that removing impediments to death is halakhically acceptable, but actively accelerating the dying process is not.

The experience of mental anguish which lessens the quality of life also carries ethical significance. Sota 46B describes the old men of Luz, a city that was inaccessible to the Angel of Death. As the men of Luz aged beyond their 'natural' lifespan, their quality of life suffered, and they became greatly depressed. Due to this depression, the men left the city and soon after died ('Sotah 46b' n.d.). The majority of rabbinic writings on this Talmudic tractate appear to support the assertion that a decreased quality of life was adequate justification for choosing to die (Tendler and Rosner 1993, sec. Quality and Sanctity of Life, a Torah View).

The two examples analyzed in this section indicate death is a permissible alternative to physical or mental suffering, but the point at which death is not only permitted but encouraged is unclear. As scientific advances continue to improve knowledge of previously untreatable medical conditions, the dying process becomes further removed from the arena of religion. Medicalization of the terminal illness experience and dying process hinders one's ability to answer the question, when can a terminally ill Jew decline medical care in favor of death?

Terminal Illness and Ultra-Orthodox Judaism: What is a Terminal Condition

The Orthodox Jewish definition of terminal illness has remained relativity unchanged since the fifteenth century. The Shulchan Aruch and the Mishneh Torah, two authoritative collections of halakhot, provide the following definition and sub-definition. A patient is deemed terefah – terminally ill - when an anatomical, molecular, or genetic abnormality, known to limit life to a year or less, is discovered. Individuals deemed terefah are still subject to all the laws, obligations, and privileges of the Jewish religion (Zoloth 1999; Bos 1994). An individual with the designation of terefah who is in extremis is deemed to be a goses. While those considered terefah can pursue therapeutic medical treatments and procedures a goses cannot, this is due to the fear that newly introduced interventions indirectly hasten death (Bos 1994; Rubenstein 2016).

Terminal Illness and Ultra-Orthodox Judaism: What are the Obligations of those Diagnosed with a Terminal Illness?

Jewish individuals diagnosed with a terminal illness are expected to take reasonable actions to maintain their health, however, UOJ rabbis do not always agree on what actions are permitted and which should be considered extreme (Eisenberg 2007, sec. Risky Treatment). (For this thesis, extreme care is considered to be a line of treatment physicians deem to be excessively risky or unnecessary given a patient's condition). Several prominent medical halakhists including Rabbi Moshe Feinstein have repeatedly stressed the fact that there is no obligation to pursue extreme medical care (Feinstein and Tendler 1996, sec. Medical care of a Patient for Whom no Cure is Possible). Despite this assertion, some members of the Orthodox Jewish faith - Rabbis Waldenberg and Auerbach among others - argue that there is no such thing as extreme care, any intervention which can increase lifespan must be employed (Linzer 2013). The fallacious arguments of Rabbis Waldenberg and Auerbach have been conflated with those of mainstream Ultra-Orthodox Judaism, perpetuating a belief that one must take any possible action to extend life.

Members of the Jewish community are not the only ones who perpetuate the belief that Ultra-Orthodox Jews must take extreme measures to maintain their health. Medical publications that examine the treatment of terminally ill Jewish patients commonly propagate this misconception (Barilan 2003; Baeke, Wils, and Broeckaert 2011). Secular scholarship highlights confusion over the use of ventilators, what treatments are/are not allowed, and even who can touch a patient (Barilan 2003; Eisenberg 2017). Many academic articles maintain a fascination with 'extreme' care while simultaneously ignoring the variety of moderate treatment options Ultra-Orthodox Jews can elect to pursue.

Orthodox Jewish Definitions of Futile Treatment

Unlike psaks which provide a relatively agreed-upon definition of terminal illness, rabbinic authorities do not agree on what, if any, criteria make a treatment medically futile. Rabbi Moshe Feinstein states that physicians are obligated to heal only if they have a medical treatment to offer (Feinstein and Tendler 1996, sec. No Possible Cure). Rabbi Eliezer Yehuda

Waldenburg - an individual whose psaks often argue contrary to that of Feinstein- argues that physicians must try any treatment even if the best outcome only results in a patient gaining a second of life (Jotkowitz 2015). This definition indicates any treatment which extends life by a literal second is considered effective. Rabbi Akiva Tatz maintains a similar position (Tatz 2010a, sec. Afterword). Many rabbis hold nuanced, non-generalizable, views on futile medical treatment, most of these opinions are derived from the work of Rabbis Waldenburg or Feinstein. This lack of consensus makes it impossible to provide one coherent definition of futility.

Medical Definitions of Terminal Illness

Contrasting the concept of terefah, the secular definition of terminal illness is not well established. The phrase ‘terminal illness’ is often used during the clinical encounter; healthcare decisions such as the use of chemotherapy, coordination of palliative care, or entry into a hospice program are mediated by the receipt of a terminal diagnosis. Despite the importance of this term, there is little agreement over its definition (Hui et al. 2012). Differences in the definition of terminal illness fall into two main categories. The first category involves characterizing a patient as terminal, what are the criteria of a terminal condition and its associated characteristics? The second involves prognostication, what disease-limited lifespan is needed to characterize an illness/condition as terminal?

Terminal Illness Points of Agreement

Current definitions of terminal illness focus on several inclusion and exclusion criteria. Physicians, legislators, and others agree over some but not all these criteria, one concept agreed upon by these parties is that of irreversibility (Hui et al. 2014). Patients can only be diagnosed with a terminal illness or condition if that condition is deemed to be medically futile, irreversible by current medical knowledge (McCartney and Trau 1990). In addition to irreversibility, there must be an established natural history and clinical progression that is known to end with death. Many physicians and scholars claim that the diagnosis of terminal illness ought to include a transition of care. This transition replaces therapeutic interventions, which are intended to halt the progression of/cure a terminal condition, with interventions that improve quality of life (Gardiner et al. 2011). Finally, many agree that cultural sensitivities are often elevated at the end of life. Increased cognizance of cultural issues is thus considered to be integral to the care of patients with a life-limiting illness (Eisenberg 2017).

Terminal Illness Points of Disagreement

While physicians, ethicists, and others agree on certain criteria of terminal illness, other prerequisites are hotly contested. The first set of disagreement involves the distinction between illnesses that can be reversed and those which cannot. This argument is predicated on the definition of medical futility. Some physicians may claim that a treatment is futile without knowledge of up-to-date outcome data (Bernat 2005). This lack of knowledge may be due to gaps in the physician’s knowledge base or due to a lack of scholarship (Bernat 2005). The nonexistence of an agreed-upon statistical threshold used to categorize a treatment as futile or efficacious further complicates an HCWs ability to diagnose a patient with a terminal illness. One camp of experts claims that a treatment is futile when it has a success rate of zero percent, others deem a treatment to be efficacious when it has a success rate above thirteen percent (Christakis and Lamont 2000; Martin and Widera 2020). Publications that advance a statistical cut-off illustrate widely discordant definitions, this variation is attributed to specialty, training, and interest in qualitative versus quantitative factors (Aghabarary and Dehghan Nayeri 2016).

A lack of data and contemporary medical knowledge forces medical professionals to evaluate an intervention's futility without complete data. The dearth of information decreases the odds a physician will correctly identify whether a treatment is or is not futile (Bernat 2005). By extension, failing to identify a futile medical intervention results in a failure to identify a terminal disease.

Terminal Illness and Expected Lifespan

There is no professional consensus on the life expectancy needed to qualify a disease as terminal. Some definitions of terminal illness require that patients have a life expectancy of fewer than two years, others require that patients are expected to live for no more than six months (Hui et al. 2014). The discrepancy in lifespan is not confined to the professional sphere. The Code of Federal Regulations states a patient must have an expected life span of less than, two years, one year, or six months, depending on the regulation cited (Bernat 2005).

Physicians are not well equipped to accurately prognosticate the lifespans of patients with a life-limiting illness. Some subspecialists are overly optimistic about a patient's prognosis. This optimism encourages patients to make important medical, social, and economic decisions under the incorrect assumption that their remaining lifespan will be longer than it is (Glare et al. 2003). An inversion of the above phenomena can also occur, certain medical specialists are overly pessimistic when predicting a patient's remaining lifespan, thus forcing a patient to organize their affairs and prepare for their death before it is necessary (van der Velden et al. 2020).

The accurate prediction of a terminally-ill patient's lifespan is not an easy task. The difficulty associated with forecasting a patient's lifespan results in doctors inappropriately recommending therapeutic or palliative treatment options (Bresnahan 1993). If physicians under or overestimate a patients' remaining lifespan while simultaneously employing a non-standardized definition of a terminal illness, treatment options presented to patients will not align with medical decisions made when the patient and doctor are provided with an accurate estimate of lifespan.

Patient Comprehension of a Terminal Illness

A tertiary issue with the definition of terminal illness is not that of consensus between medical professionals, but between patient and physician. Physicians and patients do not always employ the same definition of a terminal illness. While best practice dictates that physicians explain what a terminal diagnosis entails and then evaluate a patients' understanding, gaps in patient knowledge often remain (Epstein et al. 2016). Work by Weeks Et al. reported that 69% of patients with advanced lung cancer and 81% with advanced colorectal cancer believed that the chemotherapeutics they received were intended to cure them, while in reality these medications were used to manage symptoms and slow tumor growth (Weeks et al. 2012). Gaps in a patient's comprehension, compounded by issues of physician prognostication, results in patients pursuing treatment options that are not aligned with decisions made when one has a thorough understanding of their diagnosis and prognosis. Research initiatives and patient education initiatives have helped dispel some misconceptions of terminal illness, but others remain (Epstein et al. 2016; van der Velden et al. 2020).

Recent publications within the field of palliative care illustrate that patients who receive a diagnosis of a terminal/medically futile illness and decide to pursue palliative care achieve better outcomes than those who do not (Connor et al. 2007). Thus, the importance of accurately diagnosing a terminal illness and communicating these findings to a patient has a measurable effect on both lifespan and quality-of-life.

Rabbis and Medical Decision Making.

Ultra-Orthodox Jewish patients often consult rabbis when making healthcare decisions. These meetings help patients identify appropriate treatment options and receive pastoral care. The role of rabbis to determine the appropriateness of medical treatments is hotly debated. Some argue that rabbis should only render a decision after they speak with physicians and epidemiologists not directly involved with a patient's case (Breuer, Rosner, and Glatt 2011). This argument hinges upon the assertion that rabbis can effectively analyze the information provided by medical and scientific professionals. Others claim that rabbis should not be asked to make medical decisions, many physicians and religious authorities state that rabbis are not educated nor properly equipped to render an accurate and appropriate decision (S. Glick and Jotkowitz 2011a). The publications of Glick Et al. argue that when consulted for medical advice rabbis act as social workers who are trained to address medical and religious issues (S. M. Glick 2001). However, numerous examples of rabbis making diagnoses and treatment recommendations illustrate the inaccuracy of the social worker analogy (Hanson 2009). In certain scenarios, rabbis refer their congregants to rabbis with medical halachic training. Currently, no formal training in medical halakha exists, although if asked many rabbis could produce a roster of individuals they deem qualified to review a patient's case (S. M. Glick 2001).

It is important to recognize that there is a distinction between rabbis applying halakha to a medical query as compared to rabbis making treatment decisions for a patient. The former appears to be much more appropriate when considering a rabbi's training. A lack of formal medical training can result in poor decisions which exacerbate patient-facing concerns.

Misalignment of Therapeutic Goals Contributes to Poor Treatment Decisions

Miscommunication between members of the patient, physician, rabbi triad results in decisions that do not align with the values of the patient (Hanson 2009). Consider a physician who uses a definition of terminal illness that claims a patient will die in less than two years. When this doctor delivers a terminal diagnosis to a UOJ patient who utilizes the concept of trefah (less than a year of life) this misunderstanding affects treatment decisions and future consultation with physicians.

Occasionally, physicians who deliver a terminal diagnosis to an Orthodox Jew erroneously recommend patients pursue ‘extreme’ medical care. Rabbis may also recommend a patient pursues an extraordinary level of care if they believe the treatment of interest is efficacious. Extreme care often includes established therapies or enrollment in a clinical trial. However, a third option has recently received increased interest. The Food and Drug Administration’s Expanded Access Program allows individuals to apply for investigational new drugs outside the context of a clinical trial. Rabbis and physicians have been drawn to this program as it eliminates the need to address religious concerns related to participation in a clinical trial (Tatz 2010b, sec. Experimental Therapy and Research). Participation in this program is also recommended due to a rabbi or physicians’ belief that the IND offered is superior to any other option. While participation in this program may be considered a boon to Orthodox Jewish patients and their physicians, it is often recommended in place of other medical interventions or treatments that satisfy Jewish beliefs, specifically interventions with known risk-benefit profiles.

Chapter Four:

The FDA’s Expanded Access Program

The FDA’s Expanded Access Program (EAP) provides a pathway by which individuals can access unapproved medications outside the context of a clinical trial. In recent years members of orphan and neurodegenerative disease communities, patients with advanced cancers, and others living with terminal illnesses have expressed interest in accessing investigational new drugs (IND) via this program (Holbein et al. 2015). Academics and physicians have expressed concerns that certain patients/ populations of patients attempt to enroll in the EAP to avoid the uncertainty of clinical trials; such as receiving a placebo medication, an ineffective dose, or a possibly inferior comparator medication (A. L. Caplan and Bateman-House 2015; Van Norman 2018; Darrow, Avorn, and Kesselheim 2018). Bypassing clinical trials by enrolling in the EAP allows an individual to receive experimental medications at doses predicted to be efficacious, thus preventing the aforementioned issues (Darrow, Avorn, and Kesselheim 2018; Holbein et al. 2015). While patient advocates, pharmaceutical companies, legislators, and others have expressed support for this program, critics claim that the process by which applications to the EAP are reviewed is insufficient and non-transparent (Jerome et al. 2016).

EAP applications are sequentially assessed by three parties; pharmaceutical companies, the FDA, and institutional IRBs (Chapman, Eckman, and Bateman-House 2020). The review criteria employed by pharmaceutical companies and IRBs currently represent a ‘black box’, the standards utilized are not published. The Reagan-Udall website publishes pharmaceutical companies' EA policies, but the majority of these policies are vague. This lack of transparency, coupled with the FDA approving over ninety-five percent of EAP applications that are received from pharmaceutical companies, has forced some critics to voice their concerns. Specifically, many argue that the lack of a standardized and open review process employed by pharmaceutical companies encourages lax standards that result in patients inappropriately enrolling in the EAP (Holbein et al. 2015; Van Norman 2018). Furthermore, it is unclear if religious or social pressures - collectively referred to as non-clinical influences - are considered by these review bodies (Holbein et al. 2018). Below I examine the EAP's legislative and regulatory history to elucidate how and why these issues originated, efforts to improve the evaluation of applications, and how a continued lack of attention to patient narratives and non-clinical influences impairs the ability of application evaluators to equitably provide INDs via this program.

History of the EAP and Current Applications

The EAP and its predecessor programs advanced through several editions before the current version was established. Before the creation of the EAP, investigational therapies such as FDA-designated oncology group C medications, and medications for orphan diseases were provided on a provisional basis (Darrow, Avorn, and Kesselheim 2020). These programs worked moderately well until the AIDS epidemic (Grossman 2016, sec. The Regan Administration and INDs).

In 1983 the HIV epidemic swept through the United States of America. After the magnitude of this epidemic was understood, medications designed to treat HIV infections or manage the symptoms of AIDS entered the drug development pipeline. The first generation of medications used to treat patients with HIV/AIDS were in short supply, moreover studies designed to test the efficacy of these potential medications had stringent inclusion and exclusion criteria. The bottleneck created by low quantities of medications and small, selective, clinical trials resulted in thousands of patients being left without access to potentially lifesaving drugs. To increase access to potentially beneficial medication the FDA developed the treatment IND and parallel access programs[1], precursors to the EAP (Aids and Nichols 1991, chap. one). The treatment IND program allowed patients to receive potentially therapeutic INDs outside the context of clinical trials.

Briefly, when a pharmaceutical company applies for the study and approval of a drug, the company can request a treatment IND designation. This designation allows patients who do not benefit from standard therapy/cannot enroll in a clinical trial to receive an experimental drug outside of normal pathways. In 1987, the earliest use of this program occurred when AZT, an HIV antiviral, received a parallel pathway designation from the FDA, the application was initially filed in 1985 (Aids and Nichols 1991, sec. Modern Clinical Trials).

Three additional regulatory reforms were enacted before the current EAP was instituted. In 1997 the FDA amended section 561 of the Food Drug and Cosmetic Act to explicitly state when a patient may obtain an IND for treatment in a non-clinical trial setting. These criteria are as follows

> "if the patient's physician determines that the patient has no comparable or satisfactory alternative therapy; FDA determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug; FDA determines that providing investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and The sponsor or clinical investigator submits information sufficient to satisfy the IND requirements." (CFR n.d., pt. 21. 312)

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[1] The parallel track program is specific to medications used to treat HIV and AIDS.

A 2009 revision of the EAP restated these requirements while adding protections for pivotal trials and a clause mandating that any applications to the EAP be for a drug that is currently or was subject to an FDA IND application review. Under current regulations, there are three pathways by which an individual can apply for IND access via the EAP. The first pathway provides an IND to a single patient, this is known as a single-patient IND. Single patient INDs are most often used for patients with rare diseases such as genetic illness or cancer treatments designed for certain mutations. If a group of patients, greater than one and less than a 'widespread' group, apply for IND access, an intermediate-size patient population application is submitted. For large groups of patients, a widespread application is submitted. This last option is most often used for INDs in phase III trials that are awaiting FDA approval (Speers 2019). This thesis will mainly concentrate on INDs in pre-phase I, phase I, and phase II as these medications have a larger set of concerns related to safety and efficacy. Applications for all three EAP pathways proceed through the same review process.

Recent reports have highlighted that the aforementioned enrollment criteria are not always satisfied by individuals who received INDs via the EAP. Several pediatric gene therapies have been provided via the EAP - despite the existence of clinical trials which study participants were eligible for (Willis 2017, sec. Industry Case Study). Additionally, enzyme replacement therapies for mucopolysaccharidosis I were given to a group of patients via the EAP, instead of enrolling these patients in phase II clinical trials (Willis 2017, sec. Industry Case Study). These two examples illustrate how small cohorts of patients have received INDs via the EAP despite being eligible for clinical trials, thus sidestepping the uncertainty of these scientific endeavors. A final example of individuals enrolling in an EAP protocol instead of a clinical trial is the highly publicized receipt of INDs by Donald J. Trump and Chris Christie. Despite being eligible for ongoing clinical trials both of these men received INDs designed to treat COVID-19 infections via the EAP.

While not a concern in the cases of Trump and Christie, INDs used in early phase clinical trials are often in short supply. FDA regulations state that INDs must first be used in clinical trials, the surplus can be delivered to patients via the EAP. Scarcity of medications limits the ability of EAP reviewers to approve all suitable applications which reach their desk. The low quantity of INDs coupled with the current application review process has forced some to ask if the system by which applications are ultimately approved or denied is just and equitable (A. L. Caplan et al. 2018). Scarcity is the ultimate factor in determining if/when an IND will be delivered to a patient via the EAP.

Pharmaceutical Company Review of an EAP Application

The process to receive an IND via the EAP begins when a physician fills out a pharmaceutical company-specific application. This request is submitted to the pharmaceutical company which manufactures the IND of interest. Once an application reaches a pharmaceutical company, the patients' and physicians' materials are reviewed by a board specifically convened to review EAP-related materials. While some pharmaceutical companies use a formal board, others designate an individual or select group of individuals to independently assess an application. Pharmaceutical companies have not revealed the criteria used to evaluate IND requests, as such little is known about the review process (Varnod and Tibets 2018). This lack of clarity is concerning because review by a pharmaceutical company represents the first institutional barrier a patient must overcome to gain access to an IND.

Despite laws and policies mandating pharmaceutical companies publish the process by which EAP applications are evaluated a lack of transparency remains. The presence of a pharmaceutical ‘black box’ has been subject to scrutiny from academics, physicians, and legislators. Work by Jung et al. found that 58% of pharmaceutical companies that participate in the EAP do not publish application review policies - despite being required to by the 21st Century Care Acts (Jung, Zettler, and Kesselheim 2018). The Reagan-Udall Foundation website provides information on how pharmaceutical companies review single patient IND applications, but the scant information provided often echoes the requirements enumerated in the federal regulations which established the EAP. Johnson and Johnson Pharmaceuticals’ Jansen division is the standard-bearer for describing how an EAP application is reviewed (A. L. Caplan et al. 2018; A. Caplan et al. 2019). The transparency exhibited by Johnson and Johnson is the exception, however, and not the norm.

The continued lack of transparency exhibited by pharmaceutical companies has raised the following concerns:

1) The composition of pharmaceutical EAP review boards is unknown, forcing some to ask if review boards are composed of individuals qualified to appropriately evaluate an application. Specifically, are board members qualified to review cutting-edge research and a patient's odds of benefiting from an IND? Additionally, when considering non-clinical aspects of an application do pharmaceutical companies engage the appropriate experts to review the applications of these patients?

    This lack of transparency extends beyond the composition of a pharmaceutical companies EAP review board. Currently, companies do not report the approval, denial, or approval pending revision rates of EAP applications. A lack of data hinders outside bodies and individuals' ability to assess how often pharmaceutical companies provide an IND via the EAP.

2) Decisions to approve or deny an application are based on a pharmaceutical company's assessment of an INDs safety and efficacy. EAP application reviewers are entrusted to evaluate the risks and benefits of an IND; in this setting, the risk/benefit analysis is necessarily made using incomplete data. Data from unpublished/ongoing clinical trials are not always shared with reviewers for several reasons. Despite a lack of contemporaneous data, members of the EAP review board are often familiar with data generated from ongoing studies of the IND of interest. If incomplete or non-peer-reviewed data is referenced reviewers may not be able to accurately assess the risks and benefits an IND will confer to a patient.
3) Self-regulation can result in the generation of pressures and expectations encouraging a review board to inappropriately approve or deny EAP applications. Employees of pharmaceutical companies are not immune to social pressures. If a patient's case is well-publicized and subject to media attention EAP reviewers may elect to approve an application to avoid receiving bad press. Inversely, if a patient's risk/benefit profile favors approval of an EAP application, but concern about an adverse drug reaction (ADR) remains, an application may be denied. While the FDA states that an ADR experienced by a patient using an IND provided via the EAP can not affect ongoing clinical trials, concerns remain (Jarow et al. 2016).

This exact scenario has occurred multiple times; the cases of Sarah Broom, Josh Hardy, and others generated massive press attention, both positive and negative (Sanghavi 2013). Revisiting the example of Chris Christie and Donald J several critics questioned if INDs were supplied due to medical need or public pressure (Bateman-House and Kearns 2020).

The aforementioned examples highlight that companies consider providing INDs to be a public relations move in addition to a medical decision.

A cursory examination of the process used by pharmaceutical companies to review an EAP application highlights that the program should be subject to intense scrutiny. However, only a relatively small number of academics, regulators, and others have expressed their concerns. Jonathan Darrow, a lawyer who specializes in pharmaceutical regulation, and others have attributed the lack of concern to the involvement of IRBs and the FDA in the assessment of an application; the participation of these two bodies is thought to provide a 'check' on the system (Darrow et al. 2015; Prager 2020).

The FDA and Review of EAP applications:

After an EAP application is approved by a pharmaceutical company it is sent to the FDA. Applications for biologics are reviewed by the FDA's Center for Biologics Evaluation and Research (CBER). Applications for medical devices and other drugs are reviewed by the FDA's Center for Drug Evaluation and Research (CDER). Over 95 percent of the EAP applications that reach the FDA are approved[2] (Commissioner 2020).

The remarkably high FDA approval rates indicate two possible scenarios 1) Poor EAP applications are screened out by pharmaceutical companies before they reach the FDA, thus indicating the application evaluation process functions as desired 2) The FDA does not carefully review applications that reach their office, resulting in the approval of poorly-designed EAP protocols. A lack of data from pharmaceutical companies prevents direct analysis of the aforementioned questions, however, the following analysis of data presented in scientific

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[2] Data used for this thesis will be from pre-COVID-19 datasets in order to prevent pandemic related EAP protocols from skewing data

publications indicates that reviewers at the FDA are unable to determine the safety/efficacy of INDs provided via the EAP.

Assessment of IND Safety and Efficacy

Evaluation of several metrics reveals that the FDA is not well-positioned to accurately determine an individual's candidacy for an IND. Patient survival data, adverse drug reactions leading to clinical holds, and the decision to approve or deny an INDs approval for marketing can be used to verify the quality of the EAP application review process.

Survival data of patients who receive INDs via the EAP is only available in journal publications; no federal or private database exists. Data from unpublished EAP protocols are not accessible to the public despite directives that outcomes be recorded on clinical trials.gov. Work by Feit et al. represents one of the more comprehensive efforts to catalog the outcomes of patients enrolled in the EAP. In this single-center study, patients had a positive response to an IND 20% of the time (Feit et al. 2019). Median patient survival time after IND administration was eleven months. The increase in patient survival time was statistically insignificant, progression-free survival was four months, this was also statistically insignificant. Despite confounding variables, it appears that only one in five patients experienced benefited from INDs delivered via the EAP, these individuals did not live longer than patients who shared the same diagnosis but did not enroll in an EAP protocol (Feit et al. 2019).

The advanced disease state of patients enrolled in the EAP hampers a physician’s ability to identify IND-related adverse reactions as compared to the complications of end-stage disease. A single-site retrospective study performed by Feit et al. found that nearly 30 percent of patients who received an IND experienced one or more ADR. More concerning is the lack of clinical holds, serious adverse drug reactions often halt the administration of an experimental medication.

Despite the exceedingly high rate of ADRs, less than .5% of EAP protocols were suspended. In contrast, approximately seven percent of clinical trials are suspended due to an ADR (Feit et al. 2019). These data indicate that regulatory bodies are not well equipped to analyze an INDs safety, nor are they well equipped to determine when an ADR should pause an EAP protocol.

A tertiary mode of analysis used to examine the safety and efficacy of INDs provided via the EAP is examining the number of INDs which eventually are approved for marketing. Thirty percent of medications delivered via the EAP were approved for marketing by the FDA, however, not all medications approved by the FDA were approved for the indication listed on the specific EAP protocol (Puthumana et al. 2018; McKee et al. 2017).

Role of IRBs

When a patient's application to receive an IND via the Expanded Access Program is approved by a pharmaceutical company and the FDA, the treating physician must then submit a treatment protocol to their organization's Institutional Review Board. The role of an IRB in the EAP application process is not well defined (Chapman, Shearston, et al. 2019). There is currently widespread disagreement over the EAPs status as a research or therapy program (Van Norman 2018). Classifying the EAP as a provider of medical care, or as a medical research program, is outside of the scope of this thesis. In brief, it appears that the EAP straddles the divide between medical therapy and research, but has more features associated with care. IRBs are responsible for the assessment of research, not patient care. Thus, one is forced to ask why IRBs are involved in the EAP protocol review process.

IRBs are engaged by physicians and scientists for several reasons. Primary duties include assessing scientific validity, performing risk-benefit analysis, ensuring fair research-subject selection, and confirming informed consent forms appropriately educate patients. Within the context of the EAP, IRBs approve the treatment protocol, they also assess informed consent forms. Expanded access protocols are markedly different from the protocols normally reviewed by an IRB, as such IRBs may not have the policies or expertise needed to assess program materials.

Review of written IRB operating procedures has revealed that IRBs at academic centers and hospitals utilize markedly varied approaches when evaluating EAP protocols (Folkers and Bateman-House 2018). Some institutes require full board approval, others do not. Additionally, not all IRBs have policies that provide criteria by which to assess a protocol's appropriateness. Furthermore, many IRBs lack institutional guidelines on consulting experts who specialize in the disease or IND of interest. A lack of expert guidance hinders an IRBs' ability to appropriately assess an application. Finally, there is a lack of data that communicates how often an IRB approves or denies an EAP protocol. The absence of approval data has forced some scholars to ask if IRBs simply "rubber stamp" EAP protocols (Jerome et al. 2016). If IRBs only review informed consent forms and treatment protocols while ignoring important facets of a patient's application an unfitting decision may be reached, this issue becomes incredibly salient when exploring a patient's nonclinical motivations.

Two scholars, Alison Bateman-House Ph.D. and Holly Fernandez Lynch J.D. have repeatedly castigated the lack of written EAP policies common to many IRBs. They have also published a series of recommendations that redefine the role of IRBs within this process and recommend changes that improve an IRB's ability to manage EAP proposals.

Figure 1 Schema of the FDA's Expanded Access Program application review process. Applications require the approval of pharmaceutical companies, the FDA, and Institutional Review Boards

Continued Issues with the Evaluation of EAP Applications

Although steps have been taken to improve the aforementioned concerns a second set of lesser studied issues remain. Those responsible for reviewing an individual's application must render a decision based on their knowledge of an IND and their knowledge of an applicant's illness. Information related to a patient is limited to medical records, treatment notes, and a brief clinical narrative. Many argue clinical and medically relevant information represents one-half of a patient's materials, patient motives - which are frequently overlooked - represent the other half of an application. Johnson and Johnsons Jansen division is the only company that has recognized the value patient motives can add to the review of an EAP application. Arthur Caplan Ph.D. , the director of J&Js EAP review committee, states patient narratives would be useful to reviewers, unfortunately, physicians who submit EAP applications on behalf of their patients do not provide appropriate narrative information.

> "One consideration that CompAC wanted to use in its deliberations was what patients themselves wanted. Thus, an area marked 'patient narrative', where patients would be able to speak directly to the committee, was included on the form. The Committee

> received no narratives; more often than not the requesting physicians just copied the patient's medical history into this space, and CompAC was unable to factor in patients' expressed wishes. One reason may be that the form was not clear about what it was asking. Another is that the physicians may have been filling out the form without the patient present to provide explicit preferences." (A. L. Caplan et al. 2018)

Dr. Caplan has put into words what others have simply alluded to, the absence of a patient statement that communicates rationale for requesting an IND prohibits the examination of important non-clinical influences. Dr. Caplan has also highlighted an overlooked member of the EAP application process. Physicians are the ultimate gatekeeper of EAP applications, the information they choose to include or omit has massive implications. If patients are not able to speak directly to EAP members via a narrative statement written in concert with their physician, important facets of a patient's situation will not be considered.

A Lack of Patient Narratives Hinders the Review of EAP Applications

Currently, patient motivations to enroll in the EAP are ignored, disregarding these motivations is a disservice to both patients and the individuals who review these applications. A patient's narrative and their reason(s) for applying to the EAP provides valuable information. Physicians, employees of the FDA, and clergy who counsel terminally ill patients often stress the outsized role hope plays in a patients' decision to receive an IND. Hope in an IND if derived from a non-clinical position - as opposed to a scientific stance - results in patients developing misaligned goals (Kim et al. 2006; Hajjaj et al. 2010). For example, a patient may hope that an IND will provide a cure for their cancer, but the scientific data indicates the IND will only slow the rate of tumor growth – not reverse it. If a patient's knowledge of an IND is thought to be inaccurate, physicians or other health care professionals can re-educate and reassess a patient’s understanding.

An individual’s expectations of an INDs benefit is an abstract concept, the only tools available to determine the source of a patient’s goals are those provided by a narrative. This information ensures that the individuals reviewing an EAP application consider important non-clinical information. The value of including a patient’s motives for applying to the EAP is not readily apparent, the following vignette illustrates why this information must be included in applications.

> Two individuals, John and Bob, both have metastatic hepatocellular carcinoma (HCC). This is a terminal disease, other than palliative care there are no viable medical treatments. Both Bob and John are in their 50’s, they are married and before their diagnoses, were active and in relatively good health. Although several clinical trials are currently testing possible treatments for HCC these two men do not meet the screening criteria, their cancer has progressed too far for clinical trial participation. With the assistance of their physicians, both men apply to receive an IND via the EAP from the same pharmaceutical company. This IND is thought to prevent the growth of new tumors but will not shrink existing ones. Their applications are remarkably similar, but there is only enough surplus IND to treat one man.

Without a clinical narrative to provide additional context, it appears as if those responsible for reviewing the applications of Bob and John will make a seemingly arbitrary decision to approve one man’s application and deny the other. Supplementing clinical data with information on why these two men decided to apply for access to this IND provides additional data from which to render a verdict. Consider if a narrative statement written by Bob and his physician is included in the application, this statement claims Bob hopes this IND will prevent future tumor growth, lessening the pain he experiences before entering a hospice program. Inversely a statement written by John illustrates his interest in the IND of interest is driven by a desire to be cancer-free and return to normal life, this level of optimism, while admirable, clearly does not align with the intended effect of the IND.

John and Bobs' narratives provide important information to those responsible for reviewing their EAP applications. Bob appears to have a complete understanding of the IND, furthermore, his interest in the IND aligns with its indication, thus in this hypothetical scenario Bobs' application will be approved.

Patient Narratives are Insufficient without Appropriate Expert Guidance

Simply including narrative information is not sufficient to ensure the fair and equitable evaluation of a patient's application to receive an IND via the EAP. If the appropriate individuals do not review the narratives they will be of little value. Establishing a roster of experts to sit on pharmaceutical EAP review boards and IRBs eliminates issues such as familiarity with a disease or IND. The same approach must be taken with the review of non-clinical influences. In sum, the lack of a patient narrative has resulted in a series of blind spots within the EAP application process (Chapman, Shearston, et al. 2019; Folkers and Bateman-House 2018). Efforts are currently being made to address some issues but those related to patient motives which are derived from non-clinical influences continue to persist. The limited available data on the composition of pharmaceutical EAP review bodies indicates that few - if any - have individuals equipped to assess motivations derived from social or religious beliefs. In the case of Ultra-Orthodox Jews, a unique system of religious beliefs complicates a review board's ability to determine if patient's motivations are unique to them, driven by a religious authority, or are a-religious in origin. If the expertise of those familiar with UOJ attitudes towards end of life care is employed, important aspects of a patient's application will be evaluated in an equitable and just manner.

Conclusion

The FDA Expanded Access Program provides a valuable service to patients who are unable to enroll in a clinical trial. Unfortunately, the process by which applications are reviewed is flawed. Attempts to improve the evaluation of EAP applications have achieved mixed success, including patient narratives can further improve this process. However, narratives are of little use unless the appropriate individuals review them. The remaining chapters of this thesis examine issues with the FDA's EAP application process that cannot be solved by simply including a patient narrative, specifically those experienced when reviewing applications submitted by individuals of Ultra-Orthodox Jewish faith.

Chapter Five:

Rabbinic Arguments for Enrollment in the Expanded Access Program

The interest of terminally ill Ultra-Orthodox Jewish individuals in the Expanded Access Program is driven by several factors. Some individuals hope to avoid the uncertainty of clinical trials, others are counseled to avoid clinical trials by their rabbis. Whatever the rationale might be, patients' and their rabbi's interests and motives to apply to EAP often reveal a belief that the EAP represents a less risky avenue to receive a potentially effective medication than enrolling in phase one or two clinical trials.

Risk is a nebulous concept with many definitions and interpretations. For this chapter, risk will be considered to be the chance of a negative outcome or receipt of ineffective experimental medication. Applying this definition of risk to an Ultra-Orthodox Jewish context, adverse outcomes are comprised of both poor medical outcomes as well as the experience of mental anguish and physical suffering. There is no obligation for a UOJ individual to pursue care that is above the upper limit of acceptable risk (Gallagher 2000). To determine why EAP participation represents an acceptable level of risk to UOJ individuals, this chapter examines the rationale for avoiding clinical trials. Analysis of the attitudes of three halakhic authorities to medical risk further illustrates why participation in a clinical trial is thought to expose patients to unnecessary risk. Employing these psaks facilitates a direct evaluation and comparison of the hazards of clinical trial participation to the EAP. These same psaks will then be used to examine the potential risks and benefits of participation in the EAP.

Religious Permissibility of Clinical Trial Participation

Individuals can access experimental drugs and medical devices before they are approved for use through participation in clinical trials. However, like all medical endeavors participation in a clinical trial is not without risk (Kimmelman 2012; Kimmelman and London 2011). Those who enroll in a trial may receive an ineffective medication, a poorly performing comparator, placebo, or experience an adverse drug reaction. UOJ individuals express hesitancy in enrolling in phase one or two clinical trials due to uncertainty of outcome (Box Bayes 2013). The reluctance to enroll is directly linked to the writings of Maimonides and other Jewish thinkers: a Jewish individual is encouraged to take actions that are known to protect one’s health; but if these actions have nebulous benefits and known risks, Jewish individuals are not mandated to partake (Bos 1994; Gesundheit 2011; Tatz 2010a, sec. Limits of Risk).

The lasting influence of Maimonides's writings is readily observable in the work of Joan Box Bayes. The work of Box Bayes represents the only research effort specifically designed to identify Ultra-Orthodox motives for enrolling in or avoiding clinical trials. Interestingly, attitudes towards clinical trial participation ranged from supportive to proscriptive. According to Box Bayes, several participants claimed they would participate in clinical trials if participation confers a benefit or satisfies the duty to heal.

> “[if the study] offers a greater possibility of improving health…[there is] a duty to take part because of the teaching: ‘you have to take very great care of your life’.”

Another participant claimed they would enroll in a clinical trial because ‘you must take the risk (of participating) when there is any chance of prolonging life’(Box Bayes 2013). Improving health or lifespan appears to be the primary driver of interest in clinical trials; however, some respondents’ interest is due to the altruistic mandates of the Jewish faith. One respondent claimed they would participate in a clinical trial if the findings were of benefit to a large number of patients, thus fulfilling the duty to take care of community members. A final reason given for clinical trial participation appears to be due to a therapeutic misconception. One individual claimed enrolling in a clinical trial was ideal as ‘they [clinical trial participants] do better than the others—patients have to be monitored much more carefully' (Box Bayes 2013). If healthcare workers identify and discourage the belief that clinical trials confer benefits not available to those who receive standard care, it is unlikely high levels of interest due to this misconception will continue to exist. It is important to recognize that on average terminally ill clinical trial participants do not live longer than patients with the same condition who receive the current standard of care (Enzinger et al. 2014).

In addition to identifying motives for clinical trial participation, the work of Dr. Box Bayes examines arguments against clinical trial participation. Several participants claimed that the UOJ emphasis on the maintenance of life prohibits enrolling in early phase clinical trials: 'one must not take risks that potentially shorten life.' Risks cited included negative responses to a drug, receiving an ineffective comparator, or suffering. Interestingly several rabbis state the experience of pain is acceptable if a patient or research subject's lifespan is significantly increased as a result and the occurrence of pain does not cause suffering (Feinstein and Tendler 1996, para. Three; Prosser, Korman, and Feinstein 2012). In this scenario, the difference in pain versus suffering is determined by a self-report from the research subject (Tatz 2010, sec. Withholding treatment in chayei sha'a situations). In addition to medical arguments against clinical trials, some of the participants in the Box Bayes study expressed concern that participation in a clinical trial would infringe upon other religious obligations. Contact with members of the opposite gender, unkosher medication, and breaking observation of Shabbat were all cited as explanations for their hesitancy to participate in a clinical trial (Box Bayes 2013). Interestingly those interviewed did not cite the duty to preserve life as a legitimate reason to break Jewish law.

While many of the participants in this study provided a rationale for enrolling in or avoiding clinical trials, several claimed they were unable to make these choices without the input of rabbis, community liaisons/cultural brokers, and the input of at least three medical professionals. Unfortunately, rabbis were not included in Box Bayes study, but careful examination of halakhic literature and psaks indicates there is no one universal ruling on clinical trial participation. Dr. Rabbi Akiva Tatz and Dr. Rabbi Avraham Steinberg have written extensively on this topic and have training in both halakha and medicine. Although Tatz and Steinberg are often academic rivals who provide discordant rulings on various medical-halakhic dilemmas, both agree that clinical trial participation is a process rife with uncertainty, as such, there is no obligation to participate (Avraham Steinberg 2015; Tatz 2010a, sec. Moderate, High Risk).

As for individuals deemed terefah – a terminally ill person, not yet in the process of dying - they agree a terminally ill patient can receive a risky treatment or participate in the clinical trial if there is a reasonable chance of success (Tatz 2010a; Avraham Steinberg 1997). The aforementioned rabbis do not provide statistical thresholds for what levels of risk are acceptable and what levels are not. Instead, these rabbis reference the work of Rabbi Yitzchok Zilberstein who considers a treatment to be reasonably successful if it works at least fifty percent of the time (Minkowitiz 2019; Eisenberg 2007). Extending this logic to clinical trials both Rabbi Tatz and Rabbi Steinberg offer situational rulings. If participation in a clinical trial is thought to carry a moderate to high level of risk but there is more than a fifty percent chance of success, a UOJ individual can participate. If there is a high level of risk and low estimated efficacy participation is discouraged (Loike et al. 2010). Despite these rulings, both state that if the terminally ill individual wants to enroll in a clinical trial it is ultimately their decision.

Uncertainty, poorly defined risk/benefit profiles, and religious obligations to protect one's health appear to discourage UOJ individuals from enrolling in phase I and some phase II clinical trials. The EAP represents a pathway to access experimental therapies that carry less uncertainty, but not less risk, than clinical trials. Individuals of UOJ faith, even those deemed terefah are under no obligation to enroll in a clinical trial or apply to the EAP. However, a perceived duty to preserve and extend lifespan in addition to a perceived decreased risk burden and level of uncertainty has led to increased interest in receiving INDS via the EAP.

UOJ Risk-Benefit Analysis and the identification of Extreme Medical Interventions

When UOJ individuals consider enrolling in a clinical trial or the EAP they perform a risk-benefit analysis - or consult rabbis who perform risk-benefit analyses on their behalf - to determine the halakhic acceptability of their actions (Breuer, Rosner, and Glatt 2011). Halakha is a pluralistic endeavor, hundreds of rabbis have issued divergent rulings on the same topics; medical halakha, however, is nonetheless dominated by a select few rabbis. Rabbis Waldenberg, Steinberg, and Feinstein are three preeminent poseks who have written extensively on medical risk-taking, the identification of 'extreme' medical interventions, and the care/obligations of those deemed terefah. Halakha is an iterative process, each of these rabbis often refers to the works of past and contemporary rabbis when rendering a ruling. Despite the reliance on the same body of scholarship, the aforementioned rabbis have divergent views on what medical risks a terminally ill UOJ individual can and should take to extend their life.

Rabbi Waldenberg is an extremely conservative medical halakhist. His traditional interpretation of sources related to medical risk-taking disregards both patient autonomy and the professional judgment of health care professionals. Waldenberg claims that it is not the patient's nor their family's decision to accept or reject treatment, rather, a physician is required to extend life at all costs (Jotkowitz 2015, sec. End of Life Care). This position has led to psaks which assert that patients should maximize potential life gained and minimize potential life lost whenever possible (Jotkowitz 2015, sec. End of Life Care; Avraham Steinberg 1997). When Rabbi Waldenburg's rulings are applied to clinical trials or, alternatively, participation in the EAP, it appears that the EAP is the preferred option. Receiving an ineffective comparator, dose, or placebo all represent an "avoidable" risk. Furthermore, as clinical trial protocols are standardized clinical researchers do not have the freedom to alter the protocol or prescribe therapies that may interfere with the trial. The EAP, on the other hand, does not restrict the type of care delivered, and this program allows for potentially beneficial INDs to be delivered at predicted maximally effective doses.

Rabbi Waldenberg's insistence on the importance of extending lifespan does not extend to treating quality of life with similar reverence. According to Rabbi Waldenberg, UOJ individuals with terminal illnesses cannot receive a potential risky investigational medication designed to improve quality of life (Avraham Steinberg 1997). Unlike more permissive rabbis, Waldenberg not only permits but encourages, diminishing terminally ill individuals' *quality* of life to increase their *quantity* of life. This utilitarian approach represents a conservative school of thought that distills risk-benefit analysis down to two metrics, potential life lost and potential life gain. If a terminally ill individual wants to receive a medical intervention with high levels of risk but may gain a literal second of life the intervention should be delivered (Avraham Steinberg 1997). Gaining a literal second more of life indicates that Rabbi Waldenberg does not consider any medical intervention that increases lifespan to be extreme. Thus, UOJ individuals are obligated to apply to the EAP when a physician or rabbinic authority states this pathway provides the highest probability of increasing lifespan.

Rabbi Feinstein’s approach to performing risk-benefit analyses for terminally ill patients is quite dissimilar to Rabbi Waldenberg's. Rabbi Feinstein emphasizes the importance of minimizing suffering and improving quality of life; he claims “If a physician is unable to alleviate a patient’s suffering, just to extend his suffering life with medications, they should not do so” (Feinstein and Tendler 1996). Thus, terminally ill UOJ individuals need not expose themselves to risky procedures in order to increase their lifespan. Rabbi Feinstein also asserts that a physician’s obligation to cure the sick does not apply when a physician cannot cure the underlying disease (Feinstein and Tendler 1996). The emphasis on identifying futility indicates individuals diagnosed with a terminal illness are not obligated to receive treatments, enroll in a clinical trial, or accept an EAP protocol to manage disease progression when the risks are not commensurate with the benefits.

Unlike Rabbi Waldenberg, Rabbi Feinstein claims that a physician is obliged to alleviate the suffering of a terminally ill patient - not extend lifespan - even if doing so generates avoidable risk. This position challenges the previous assertion that terminally ill individuals need not pursue risky medical interventions that slow but do not stop disease progression. It is important to recognize that if a patient expresses interest in an IND which is predicted to slow disease progression, which will in turn decrease suffering, Rabbi Feinstein’s rulings indicate enrolling in an EAP protocol or clinical trial is an acceptable action. Interestingly, Rabbi Feinstein never explicitly endorses the doctrine of double effect but writes that if a terminally ill patient requests access to medication that will decrease suffering but may hasten death the medication can be given. The inverse also holds a patient can refuse medication even if doing so will increase their lifespan. These two psaks indicate enrolling in the EAP is permitted, even if the IND of interest is potentially life-limiting (Jotkowitz 2014).

The work of Rabbi Feinstein does not explicitly encourage or discourage participation in a clinical trial or the EAP. Rather, Rabbi Feinstein allows the terminally ill individual or their family to make the final decision (Jotkowitz 2013). If the sick individual claims they can tolerate the mental anguish that comes from clinical trial participation (e.g., they learn they were in the control arm, received an ineffective dose, or comparator), they should be allowed to do so (Jotkowitz 2014). If the specter of clinical trial-related uncertainty would be overwhelming, the individual can elect to apply to the EAP. If neither option appeals to the patient, they are under no obligation to enroll in a clinical trial or the EAP. Rabbi Feinstein's methodology represents a collaborative effort - patients, healthcare professionals, and rabbis are all expected to contribute to this important conversation. Each party's concerns are considered and weighed in comparison to possible benefits. This tactic does not consider increasing lifespan to be the sole goal; quality of life is very important. Unfortunately, Rabbi Feinstein does not provide a statistical threshold of risk or benefit from which to make a final determination. It appears that the level of acceptable risk is situational and wholly dependent on the terminally ill individuals' goals i.e., decreased suffering, increased life span, etc.

Unlike Rabbis Waldenberg and Feinstein, Rabbi Dr. Steinberg M.D. employs a combination of halakha and quantitative techniques to determine what medical interventions should be pursued and which should not (Avraham Steinberg 2015). According to Rabbi Steinberg, the delivery of medical care, enrollment in a clinical trial, or enrollment in an EAP protocol is contingent upon a mortality risk of less than 30 percent (A. Steinberg 1994; 2001). Additionally, a benefit must be predicted to occur at least 50 percent of the time. The exact cut-off for identifying acceptable experimental treatments or procedures shifts with the patient's reasons for pursuing a medical intervention. If a highly risky procedure has a high probability of alleviating suffering, patients are often encouraged to pursue said treatment. When medical interventions do not satisfy the aforementioned risk-benefit parameters, Dr. Steinberg asserts that the treatment must be considered extreme and should be avoided (A. Steinberg 2001). If both the EAP and a clinical trial are of interest to an individual, Dr. Steinberg's scholarship indicates one should attempt to minimize risk. Thus, the preferred decision seems to be enrolling in the EAP as a risk mitigation strategy. This risk-benefit approach parallels the ethical principle of proportionality often utilized by secular bioethicists (Hermerén 2012). Unfortunately, quantifying the risk of participation in a clinical trial or enrolling in the EAP is an incredibly challenging undertaking (Chen and Kim 2016). As such physicians and rabbis appear to arbitrarily quantitate the risk-benefit profile of medical interventions and experimental treatments.

Halakic Risk-Benefit Analysis of Participation in the EAP

There is no singular goal that persons living with a terminal illness hope to achieve by enrolling in the EAP. Patients may wish to experience less severe symptoms, a momentary pause of disease progression, or in very optimistic cases a cure/remission. The desire for palliative or curative benefits will change the level of risk a patient is willing to be exposed to. In the case of Ultra-Orthodox Jewish patients, some may be willing to expose themselves to extreme risks to achieve a modest benefit. Patients must recognize that administration of an IND does not guarantee a therapeutic benefit. If physicians, rabbis, and patients discuss their goals and expectations of an IND then Ultra-Orthodox Jewish patients who subscribe to a risk-averse approach, as described by Dr. Steinberg or Rabbi Feinstein, may identify modes of care outside of the EAP that align with their beliefs and goals.

Consider the work of Feit et al. which revealed that only one in five patients received an IND to which their cancer responded; of those who had a positive response, the median time of survival was less than a year, 11.4 months (Feit et al. 2019). Applying Steinberg's risk-benefit analysis to this data indicates participation in the EAP is at the upper limit of acceptable risk as clinical benefit is experienced less than 50% of the time. Furthermore, Feit reports that 35% of adult patients experienced a serious adverse event (Feit et al. 2019). This risk appears to be above the level that is normally tolerated by Rabbis Feinstein or Steinberg, but is deemed acceptable by Rabbi Waldenberg. Modifications of acceptable risk exposure are predicated upon a patient’s goals. Conversation between the patient, physician, rabbi, and others can identify these goals, thus supplementing the information that is considered when determining the halakhic acceptability of a patient’s decision to enroll in the EAP. Any patient goal and the accompanying rationale communicated during these conversations must be included in the patient narrative submitted to EAP committees. Information provided in the narrative, will allow reviewers to evaluate important non-clinical information such as religious motives.

Patient Narratives and the EAP

When reviewing applications to the EAP including a patient narrative will provide important information that is otherwise inaccessible to members of a review panel. These narratives include details such as the origin of the applicant’s interest in an IND and the desired outcome from an IND. If an individual of UOJ faith provides a narrative, religious beliefs, halakha, and the opinion of their rabbi will likely be referenced (Jotkowitz 2013). Evaluating EAP applications that include UOJ religious or social motivations is a formidable challenge for those without appropriate training. Professionals such as Dr. Bateman-House have recognized the need for religious expertise, but to date, religious experts have not been added to EAP application review boards. Currently, review committees are ill-equipped to evaluate applications submitted by UOJ individuals. Lack of expertise increases the odds of an unjust and by extension unequitable decision to provide or prohibit delivery of an IND.

Ensuring fair evaluation of a UOJ individual's application materials requires a rabbi or professional with knowledge of halakha and Jewish medical ethics. Educating members of a review board on the basics of the UOJ faith and medical decision-making at the end of life will provide important background information. However, this information is not sufficient to make an informed evaluation of an application. The sheer volume or variety of rabbinic writings, responsas, and nuanced halakha that may be referenced in a patient’s application materials can be efficiently identified by a rabbi. Once the source of a patient’s interest or motivation to enroll in the EAP is identified rabbis can determine if they align with the decisions of prominent medical halakhists. If the works of Rabbi Feinstein, Steinberg, Waldenberg, Tatz, or other Jewish thinkers are referenced, the rabbi can compare the writings of these rabbis to the patient’s narrative, ensuring homology and an accurate interpretation of halakha. Furthermore, the reviewing rabbi can speak to the applicant and their rabbi to clarify questions that may arise during the review process. When the application review process indicates religious motivations that would not be satisfied by the IND of interest, the rabbi can work with the patient and their spiritual counsel to identify medical options that better align with their physical and religious needs.

Including rabbis with training in medical halakha will ensure other members of EAP review committees understand where a patient’s interest in an IND originates from and if this interest aligns with the possible indications of an IND. Maintaining a roster of these experts will allow review committees to access expertise that results in the fair and just allocation of scarce

INDs. If an application indicates a UOJ applicants’ interest in an IND does not merit approval these medical and religious experts can examine and recommend religiously permissible treatment alternatives.

Chapter Six:

Halkahically Permissible Alternatives to EAP Participation

Those familiar with the FDA’s Expanded Access Program have described the program as the final pathway by which individuals with a medically futile condition can access potentially effective medications or medical products (A. L. Caplan and Bateman-House 2015; A. L. Caplan et al. 2018; Chapman, Moch, et al. 2019). Those who attempt to enroll in this program have tried all approved medicines and are unable or, in some circumstances, unwilling to participate in clinical trials. For individuals of UOJ faith, interest in the EAP is derived from an obligation to maintain health as well as the psaks of rabbis which encourage actions to increase both life span and quality of life. When medical-halakhists issue a ruling on the risks and benefits of extraordinary medical care, such as the EAP, they often explore the topic as an isolated matter (Zohar 2010, sec. Differing Extent of Aims and Effects; Bleich 1993, sec. Hazon Ish on textual emendation). Seeing as most religiously informed discussions on EAP participation do not consider alternative treatment options, rabbis have not provided halakhically viable alternatives. One alternative to EAP and clinical trial participation is palliative care. Palliative care is both religiously permissible and confers more benefits with fewer risks than INDs provided via the EAP.

Palliative care occupies an ambiguous space within the UOJ faith. Jews are prohibited from taking actions that hasten death but are allowed to forgo actions that may lead to the experience of suffering; as such most poseks claim palliative medicine is only to be pursued when other treatment options are exhausted (Baeke, Wils, and Broeckaert 2011). By examining the benefits of palliative, interventions I demonstrate that this type of care is a legitimate medical treatment. Establishing the medical benefits of palliative care provides the foundation from which the religious permissibility of palliative care is supported. Arguments I advance in this chapter illustrate that recasting palliative care as a medical treatment, as opposed to an admission of failure and futility, indicates that UOJ patients should be urged to consider this form of treatment when they express interest in the EAP.

Palliative Care Improves both Quality and Quantity of Life

Quantitative research within the field of palliative care is a relatively recent development. In the past, informal conversations with patients and clinical anecdotes provided by health care workers supplied the information needed to evaluate the efficacy of new medicines or care strategies (Milligan 2009, sec. The Need for Palliative Care Research). Many criticized this approach as it does not follow the evidence-based practices common to other fields of medical research. In response to these criticisms palliative care specialists integrated the tools of evidence-based medicine into research on end of life care (Farquhar, Ewing, and Booth 2011). Studies completed after this shift illustrate that the tools of palliative medicine not only improve quality of life but in certain scenarios increase lifespan (Bakitas et al. 2015; Temel et al. 2010).

Patients diagnosed with a terminal illness who receive palliative care experience better outcomes than those who enroll in clinical trials or the EAP (Peppercorn et al. 2004; Bakitas et al. 2015). The work of Enzinger et al. found that individuals diagnosed with terminal cancer who participated in phase I clinical trials experienced a significant increase in aggressive end of life care and later enrollment in hospice programs - an indirect measure of decreased quality of life (Enzinger et al. 2014). This study also reported a significant increase in ICU and hospitalized deaths, as opposed to deaths at home which are largely preferable (Enzinger et al. 2014). Most importantly research subjects experienced a significant decrease in quality of life near death (Enzinger et al. 2014). Additional research has found that early integration of palliative care into phase I and II oncology clinical trials significantly improved research subjects' quality of life and in certain scenarios, significantly improved lifespan (Temel et al. 2010; Bakitas et al. 2015; Bauman and Temel 2014).

Various studies have shown that terminally ill individuals who enroll in clinical trials often experience a decrease in quality of life. Currently, few studies have examined quality of life in EAP participants, but the small body of scholarship indicates EAP participation does not result in improved life quality. The work of Feit et al. illustrates that individuals enrolled in the EAP are unlikely to experience a significant increase in lifespan. Furthermore, twenty-seven percent of EAP participants included in this study experienced an ADR, indicating that almost one-third of participants experienced an event known to decrease quality of life (Feit et al. 2019). These data indicate that palliative care programs may confer more benefits and fewer risks than participation in the EAP or clinical trials.

Some critics of palliative care research claim these programs are unable to consistently increase lifespan, thus requesting an IND via the EAP or enrolling in a clinical trial represents a better option to receive treatments that possibly extend lifespan. Recent research efforts which address this criticism demonstrate that early integration of palliative care consistently improves quality and quantity of life. Schuman et al. found that early enrollment of palliative care, when coupled with the standard of care significantly improved both quality and quantity of life, as compared to patients who only received standard of care (Rowland and Schumann 2010). Publications by Lynch, Schuman, and others indicate that enrolling in palliative care within three weeks of receipt of a terminal diagnosis improves the quality of life and lifespan (Earle et al. 2008; Zimmermann et al. 2008; Kavalieratos et al. 2016). Despite these findings many patients are hesitant to receive end of life care due to commonly held misconceptions, and a lack of knowledge about this type of medical care.

One tool to improve awareness of the benefits of palliative care is patient education as an examination of patient hesitancy to enroll in palliative care reveals that there is a widespread misconception of the tools and goals of this form of treatment. A population-based study that examined the underutilization of palliative care found that more than half of respondents had a poor understanding of palliative care (Flieger, Chui, and Koch-Weser 2020). Extending this line of inquiry to the specifics of hospice and palliative care a national study conducted by Koch-Weser and colleagues reported that 44% of study respondents associated palliative care with death and 38% conflated hospice with palliative care (Flieger, Chui, and Koch-Weser 2020). Fortunately, misconceptions or misunderstandings of these modes of medical care can be corrected with patient education, educating patients also increases willingness to enroll in palliative care (Kozlov, Reid, and Carpenter 2017). Notably, individuals who display an understanding of palliative care are also more likely to agree with the position that palliative care is an effective treatment option.

Reframing Medical Interventions as Palliative Shifts the Definition of Medical Futility

A medication or intervention is considered to be futile when there is no reasonable hope of a cure or benefit. Physicians often debate the definition of futility, specifically what benefits or lack-there-of are needed to classify an intervention as futile (Aghabarary and Dehghan Nayeri 2016; Bresnahan 1993). Although this debate is ongoing a commonly used definition is “the desired outcome that a therapy will benefit a patient will not occur, based on the best available evidence” (Goldberg 2020). When applying this definition to possible treatments for terminally ill patients, a patient’s therapeutic goals will help to designate a treatment as futile or viable. Consider palliative chemotherapy, if a terminally ill patient requests chemotherapy to manage pain or other symptoms the desired effects appear to align with a secondary indication of the medication. However, if a patient with a terminal illness requests a chemotherapeutic agent to achieve remission their goals are futile.

If medications or interventions are deemed futile because they cannot cure a condition, recasting them as palliative may reveal a second set of benefits. Studies of palliative chemotherapy, surgeries, and other medications/interventions have shown that when appropriately delivered study participants experienced improved quality and quantity of life (Kavalieratos et al. 2016). When compared to the nebulous benefits and risks of participation in the EAP or a clinical trial palliative care is a known quantity. Early enrollment in palliative care is a medical treatment unto itself, by communicating the benefits of palliative care patients and their families can consider the risks and benefits of palliation in comparison to clinical trials or the EAP.

With regards to the EAP, patient narratives provide the information needed to determine if medications that are deemed futile when delivered with curative intent, can be used in a palliative context. A careful review of patient motives allows the treating physician as well those involved in the application review process to identify care plans that meet patient goals and when appropriate preempt the need to enroll in the EAP. Furthermore, if a patient applies to the EAP and is awaiting a decision - which takes 30 business days in non-emergency situations – palliative care can be initiated to ensure a patient is comfortable while awaiting the IND. (CDER and CBER 2016, sec. When can treatment begin under expanded access protocols not for emergency use?) Thus, the waiting process is an opportunity to further educate patients on both the IND they will be receiving as well as the palliative care they are currently receiving.

Finally determining patient motives and their desire for an IND provides valuable information if the IND received is deemed ineffective. If patients receive an IND that does not achieve its primary objective, they can transition back to palliative care, or continue using the IND if it provides palliative benefits.

Ultra-Orthodox Judaism and Palliation

The misconception that UOJ patients are not “supposed to give up [on life]” is perpetuated by both health care workers and Jewish individuals (Kinzbrunner 2004). The goals of palliative care are not antithetical to the Jewish religion: this form of medicine can address spiritual and emotional concerns while simultaneously improving the quality and quantity of life. This author's examination of palliative care’s halakhic acceptability helps reframe it as a legitimate set of medical tools. Additionally, by mapping the benefits of palliative care onto the psaks of Rabbis Waldenberg, Feinstein and Steinberg I elucidate why and how these programs are halakhic permissible.

As examined in the previous chapter, Rabbi Waldenberg is a rather conservative rabbi who states terminally ill individuals may expose themselves to high levels of medical risk if there is a non-zero chance that doing so will increase their lifespan (Jotkowitz 2015). This ruling appears to be absolute, however, an examination of psaks related to uncertainty, specifically medical uncertainty, provides a position from which enrollment in a palliative care program can be supported. *Safek* or uncertainty is a common subject within the Talmud. Various rabbis have ruled that when presented with two options, one with a more certain outcome and one that is more nebulous, the more certain option should be taken in all but the most exigent of circumstances (Eisenberg 2007; Brody 1983). Rabbi Waldenberg's writings on end of life care indicate one can expose themselves to risk via the EAP to extend lifespan, even though INDs provided via the EAP have poorly defined risk-benefit profiles. The work of Feit et al. indicates it is unlikely that a terminally-ill individual will experience a significant clinical benefit from an

IND which is in phase I or II trials. Therefore, when comparing EAP participation with palliative care – which has well-defined risks and benefits – it appears that Waldenberg's work can be interpreted to support palliative care as the more appropriate option to take (Feit et al. 2019). If Waldenberg's primary and only interest is truly increasing lifespan, the certainty of palliative care indicates it is a halakhically permissible option for patients diagnosed with a terminal condition.

Rabbi Moshe Feinstein is the author of a massive body of medico-halakhic rulings. Close examination of his writings on end of life care and terminal illness illustrate that he prioritizes quality of life over quantity of life (Prosser, Korman, and Feinstein 2012). Patients need not suffer to increase their lifespan. In an examination of medical futility and the role of the physician, Rabbi Feinstein eloquently states that when all treatments are deemed to be medically futile the role of the physician transitions from a medical professional who cures to a caregiver who comforts (Kinzbrunner 2004). One of the goals of palliative care is to decrease patient suffering; this goal closely aligns with Feinstein's work.

In addition to halakha on medical risk-taking at the end of life, Rabbi Feinstein has written extensively on false hope within a medical setting. False hope, which is defined as hope without justification, is commonly experienced by individuals diagnosed with a terminal condition and their family members (Garrard and Wrigley 2009). Rabbi Feinstein is incredibly sensitive to the issues that may arise due to the experience of false hope, specifically the experience of emotional distress. If a patient has false hope in an experimental medication they are receiving and then learns it is not working, the resulting mental suffering may greatly decrease their quality of life (Feinstein and Tendler 1996, sec. Mental Anguish). Eliminating false hope in an IND in advance of administration will negatively impact a patient, but this experience will be less severe than a patient learning they have received an ineffective IND after administration. Thus, if a patient is interested in the EAP, but claims they will not be able to tolerate the possibility that the IND provided is ineffective, palliative care is a halachically viable alternative.

A final halakhic framework that justifies enrollment in a palliative care program, as opposed to participation in a clinical trial or the EAP, is that employed by Rabbi Steinberg. Rabbi Dr. Steinberg uses a quantitative approach to determine the halakhic acceptability of medical interventions. As examined in Chapter Five, Steinberg claims the delivery of medical care, enrollment in a clinical trial, or enrollment in an EAP protocol is contingent upon a mortality risk of less than thirty percent. Additionally, a benefit must be predicted to occur at least fifty percent of the time. As compared to participation in the EAP or clinical trials, palliative care has a very low incidence of unanticipated medical emergencies (Schrijvers and van Fraeyenhove 2010). This type of medical care also confers benefits, such as improved quality and quantity of life more frequently than clinical trials or the EAP. Ultimately Steinberg’s position on palliative care is situational when a patient expresses a desire to enroll in the EAP individuals familiar with the patient's case must determine the level of risk, predict if the benefit is higher or lower than enrollment in a palliative care program, and make appropriate recommendations.

In sum, there is no ‘correct’ halakhic ruling which identifies either palliative care or experimental treatments as the preferred approach to end of life care. Examining a patient’s understanding of palliative care, specifically within a religious context, and educating them on both palliative care and the IND of interest ensures an informed decision is being made. Ultimately, this decision must be respected by HCWs and those involved with the EAP.

Chapter Seven:

Discussion

The purpose of this thesis was to show how terminally-ill individuals of UOJ faith utilize the FDA’s Expanded Access Program to bypass the uncertainty of clinic trials. Before exploring issues directly related to the EAP, this thesis reviewed the UOJ approach to end of life care and the maintenance of health. My examination of Talmudic tractates, rabbinic writings, and the work of contemporary poseks illustrates that the UOJ obligation to protect life begins long before the diagnosis of a terminal illness. Individuals are expected to exercise the ‘prudent man’ standard when making low-risk health-related decisions, in situations of high risk they consult their rabbis (Breuer, Rosner, and Glatt 2011; S. Glick and Jotkowitz 2011b).

With regards to high-risk situations, rabbis consider both the halakhic and scientific validity of treatment plans. Seeing as a rabbi’s congregants hold them in high regard – rather pious rabbis are thought to represent the living word of G-d – medical advice provided by a rabbi is frequently respected and prioritized over the recommendations of healthcare providers (Hanson 2009). Adherence to the teachings and decisions of rabbinic authorities leads some terminally-ill individuals of the UOJ faith to try to enroll in the FDA’s Expanded Access Program.

The FDA’s Expanded Access Program represents a departure from the U.S Government’s traditional drug approval process. From its inception, this program has provided terminally-ill patients with potentially effective experimental medications outside of the context of a clinical trial. As interest in this program increased, the FDA established screening criteria that patients must satisfy before receiving access to an IND. Although the United States Government has established a series of rules and recommendations related to the review of applications to the

EAP, pharmaceutical companies and IRBs have been slow to integrate these changes (Folkers and Bateman-House 2018). The lack of transparency exhibited by pharmaceutical companies and IRBs is a point of concern. Specifically, who is reviewing these applications; is the review process standardized; and how can the applicant be assured a just and equitable decision has been reached? In my opinion, these questions have not been satisfactorily answered and require further exploration.

To ensure that both clinical and non-clinical factors of an EAP application are considered, Dr. Arthur Caplan and others recommend the inclusion of a patient narrative (A. Caplan et al. 2019; A. L. Caplan et al. 2018). They claim close review of a patient narrative will enable application reviewers to make equitable and just decisions when allocating scarce INDs. I argue the inclusion of a narrative is not sufficient on its own - appropriate professionals need to evaluate these narratives. When examining materials submitted by patients with unique social or religious beliefs, such as individuals of Ultra-Orthodox Jewish faith, it is imperative that scholars familiar with the laws and teachings of this religion are employed. Although some pharmaceutical expanded access review committees have recognized the need for religious expertise, to my knowledge none have established a position for members of the clergy or academics with training in religion or religious ethics.

Individuals of the UOJ faith and their rabbis express interest in the EAP for multiple reasons. Some are specifically interested in INDs which are delivered via this program, whereas others express concern about the risks of phase I and II clinical trials. Close examination of the works of Joan Box Bayes and Rabbi Dr. Akiva Tatz illustrate that there is no singular reason why UOJ individuals attempt to avoid clinical trials, but it appears many UOJ individuals want to avoid the uncertainty inherent in clinical trials. Individuals of UOJ faith express interest in medical treatments that decrease uncertainty and maximize the possibility of a positive outcome (Box Bayes 2013; Tatz 2010a, sec. Experimental Therapy and Research). Avoiding clinic trials eliminates uncertainty related to dosage, inferior comparator medications, and placebos; whereas receiving INDs via the EAP ensures that participants receive an experimental medication at its predicted maximally-effective dose. Furthermore, individuals enrolled in the EAP do not need to follow a standard treatment protocol. Thus, there is no constraint on medications that can be used in conjunction with the IND of interest. Risk mitigation and the lack of restrictions on treatments indicate why certain individuals believe receiving an IND via the EAP satisfies halakhic mandates and is superior to other treatment options.

In addition to concerns related to clinical trials, religious obligations to maintain and extend lifespan or quality of life encourage EAP participation. Certain rabbis, such as Rabbi Waldenberg, have issued conservative rulings which claim an individual of UOJ faith must attempt to increase their lifespan, even if doing so only results in a literal second of additional lifespan (Jotkowitz 2015). Thus, individuals who adhere to this school of thought utilize the EAP to access INDs which can potentially increase lifespan. Other rabbis who have also received medical training, such as Rabbi Dr. Steinberg, employ a quantitative approach that permits EAP participation if the risks are commensurate with possible benefits (Avraham Steinberg 2015; 1997). A final approach, advanced by Rabbi Moshe Feinstein claims patients are under no obligation to enroll in clinical trials or the EAP due to the medically futile and terminal nature of their illness (Jotkowitz 2014, sec. End-of-life care). Despite this ruling, Feinstein's psaks do not prohibit clinical trial or EAP participation; it is ultimately the patient's choice.

Interestingly, the positions advanced by Rabbis Waldenberg, Feinstein, and Steinberg can also be used to justify the receipt of palliative medications. Historically, individuals of the

UOJ faith did not seek out palliative care as it was thought to be antithetical to the obligation to maintain and extend lifespan (Bressler and Popp 2018). Recent quantitative research has shown early enrollment in palliative care increases both quality and quantity of life, thus indicating it is a viable treatment option for individuals of the UOJ faith (Bakitas et al. 2015; Bauman and Temel 2014). This form of care appears to provide beneficial outcomes on a more consistent basis than INDs provided via the EAP. The certainty of outcome and ability to improve both lifespan and quality of life satisfies the criteria advanced by Rabbis Waldenberg and Feinstein. The religious acceptability of palliative care indicates that UOJ individuals who express interest in the EAP be educated on this alternative mode of treatment by a rabbi and physician.

Recommendations to Improve the Review of Patient Narratives

When appraising EAP applications, employing a framework that evaluates secular ethical principles with an ability to accommodate religious values ensures all applications are equitably reviewed and INDs are delivered in a just fashion. Understandably, there are few frameworks designed to compare religiously-informed patient requests to secular ethical principles. James Buryska, a chaplain, and clinical ethicist at The Mayo Clinic developed an approach from which one can assess the ethical weight of a patient's cultural, religious, and spiritual claims. The framework advanced by Buryska is unique as it does not prioritize secular or religious principles. Through a series of five questions, Buryska simply asks if a religious patient's request is both internally and externally defensible (Buryska 2001).

Internal (religious) defensibility asks can an individual's claim withstand scrutiny which originates from within the religion? External defensibility asks can the religious claims withstand scrutiny from competing secular ethical principles? It is important to recognize that classifying a claim as internally and externally defensible is not a wholesale endorsement of a patient's request. After establishing both internal and external defensibility, the patient's claim is compared to "claims based on the skill, authority, and judgment of the physician; on the rights or sensibilities of others; on legal considerations; on economic realities and issues of distributive justice"(Buryska 2001).

Concerning the EAP, information provided via the patient narrative must be evaluated by appropriate experts. Following evaluation, salient religious concerns are mapped onto the Buryska framework described above. Religious or social claims can then be considered in comparison to other secular factors. This examination facilitates the prioritization of salient ethical concerns and the formulation of an equitable decision. Importantly it does not prioritize religious or secular features, ensuring applications are not approved due to a misunderstanding or inability to analyze religious claims.

Chapter Eight:

Concluding Remarks

Close analysis of Talmudic tractates, medico-halakhic writings, and the work of prominent rabbis indicates that there are multiple UOJ approaches to the management and treatment of a terminal illness. Rulings by traditionalist rabbis maintain that one must attempt to maximize their lifespan; these verdicts appear to support enrollment in the EAP. Conversely, other poseks permit terminally-ill patients to avoid clinical trials or the EAP, thus prioritizing quality of life. These two options appear to be in direct contradiction. Via the lens of halakha, reconceptualizing palliative care as a series of life-extending medical interventions indicates palliative care must be considered when caring for terminally-ill individuals of UOJ faith. Improvements within this field demonstrate that early delivery of palliative care improves both quality and quantity of life. Furthermore, this is a well-characterized treatment option with well-defined outcomes, unlike the nebulous results of EAP participation. Thus, this treatment option satisfies halakhic criteria and should be offered to individuals who follow either traditional or liberal schools of Jewish thought.

In addition to topics directly associated with the Jewish religion, this thesis has shown that improving the process by which EAP applications are evaluated requires more than the inclusion of a patient narrative, it also requires appropriate expertise and an approach that considers both social and medical factors. Failing to acknowledge and address a patient’s unique lived experience invalidates important aspects of an application. Retaining trained experts ensures all features of an application are equitably assessed, thus leading to the fair allocation of INDs.

Finally, through an examination of halakha and data from EAP protocols, this thesis shows that identifying a treatment as halakhically acceptable does not automatically make it the ideal medical intervention. The Jewish legal system is intimidating; currently medical professionals and those involved in the conduct of clinical trials or the EAP are unable to tease apart secular and religious claims found in a patient's application. Employing an individual with an understanding of medical-halakha enables the identification of applications that are both religiously and medically appropriate. Applicants that only utilize religious defenses when attempting to bypass clinical trials should not be provided INDs, as this leads to the inequitable rejection of applications made by other patients with a demonstrated need. The same approach must be taken with any application that presents unique social or non-clinical dimensions. Accepting applications that do not wholly satisfy the EAPs screening criteria is a failure of both religious and secular ethical mandates.

The late Rabbi Dr. Jonathan Sacks asserts that at its core, the Jewish faith is a religion that emphasizes collective responsibility. This responsibility extends beyond members of the Jewish community to all members of an individual's community, and ultimately the world (Sacks 2007). Those diagnosed with a terminal illness are not exempt from this responsibility, persons of the UOJ faith must consider their families, HCWs, members of the community, and others diagnosed with the same illness when making decisions at the end of life. Ultimately decisions regarding enrolment in the Expanded Access Program can be defended via the lens of halakha but ignoring other treatment options and obfuscating one's true motives behind Jewish law is a disservice to patients, health care workers, and religious leaders.

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