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Doctorate Proposal

A MANUALISED POST-TRAUMATIC GROWTH INTERVENTION FOR PEOPLE WITH HEMATOLOGICAL CANCERS IN GREECE

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INTRODUCTION

Leukemia and its treatment can severely impact the individual's body (e.g. hair loss, mouth sores, infection, diarrhoea, nausea, vomiting, rash, fatigue, neuropathy, organ damage) (Crossnohere et al., 2019), social interactions (e.g. loneliness, protective isolation, lack of freedom) (Biagioli et al., 2017) and psychological state (e.g. depression, anxiety, fear of cancer recurrence) (Barata et al., 2016). Such experiences can be traumatic for some people.

In this context, trauma is defined as "*a set of circumstances that challenge an individual's safety, identity and future*". These circumstances are accompanied by significant challenges to the resources of the individual, including the fundamental components of the way an individual understands the world, their place in it and assumptions like the benevolence, controllability and predictability of the world (Tedeschi & Calhoun, 2004).

People deal with cancer and its potential trauma in different ways. A review of 73 models developed through qualitative studies (Boutillier et al., 2019), established a framework that summarizes the process of living with and beyond cancer into three elements. This includes Adversity, Restoration and Compatibility (ARC). These elements respectively refer to the impact of cancer, readjusting to life and reconciling with cancer. Adopting ARC allows this doctoral dissertation to have a conceptualizing framework that is common with other studies as it frames the diverse experiences of people with cancer.

Nevertheless, such traumatic events like experiencing cancer have been proposed to provide individuals with an opportunity to grow and experience what is known as **post-traumatic growth** (PTG) (Tedeschi & Calhoun, 2004). Boutillier et al. (2019) in particular mention that some of the traumatic effects of cancer can be found in the Compatibility stage of someone's journey through PTG. The ARC framework in particular is compatible with PTG, as it encompasses the dynamic and non-linear process of PTG (Tedeschi & Calhoun, 2004).

POST-TRAUMATIC GROWTH

Post-traumatic growth is defined as "*the positive psychological changes following a traumatic life crisis*" (Tedeschi et al., 2018). People who have experienced extraordinary or traumatic events tend to present with more PTG than those who have not (Tedeschi & Calhoun, 2004). This means that PTG is possibly linked to adversity. PTG is different to the concepts of resilience, hardiness, optimism and coherence. These concepts describe personal traits that allow people to manage adversity well. Differentially for PTG, it is the individual's struggle in the aftermath of trauma that is critical, not personal traits. Similarly, PTG is occurring to a greater degree than any that would be expected as a normal part of development and PTG is

occurring alongside the negative impact of the trauma (Tedeschi et al., 2018). PTG has been measured across five domains: relationships with others, new possibilities in life, perception of themselves, spiritual change and life appreciation (Tedeschi & Calhoun, 1996).

PTG has been reported as positive changes in several facets (Tedeschi & Calhoun, 2004). For example, reported changes in self may include how individuals perceive themselves, becoming a better person, feeling stronger, more self-assured and being more assertive. A changed sense of relationships with others could entail closer and deeper relationships, more positive relationships, handling of relationships better, better utilization of social support and increased sensitivity to others. A changed philosophy of life may comprise of increased appreciation of life, changes in priorities, straightening of spiritual beliefs and altering basic assumptions about life.

A functional model of PTG has been proposed by Tedeschi and Calhoun (2004). It connects elements like, who the person was before the traumatic (seismic) event, the challenges they face, the level of rumination, self-disclosure and distress affect the development of PTG. This model was expanded to include the outcomes of PTG, the co-existence of distress with PTG and why some people do not experience PTG; because their core beliefs are not challenged (Tedeschi et al., 2018; see Fig.1). Overall, the PTG field is not a problem-focused one but a strengths-based one.

Notably, PTG does not only seem to be affecting the individual who has experienced the trauma, but also the people around them, like their family or even health care professionals. This is known as vicarious PTG (Manning-Jones, et al., 2015). For example, a study in Greece found that health care professionals working with people suspected of COVID-19 infection experienced vicarious PTG particularly in the areas of personal strength and appreciation of life (Kalaitzaki et al., 2021). At the same time, the role of the family has been highlighted in the field of PTG. Specifically, an addition to the PTG model of Tedeschi and Calhoun (2004) was suggested to demonstrate that the family is not only the setting in which PTG takes place, but is also part of the PTG process (Berger et al., 2009).

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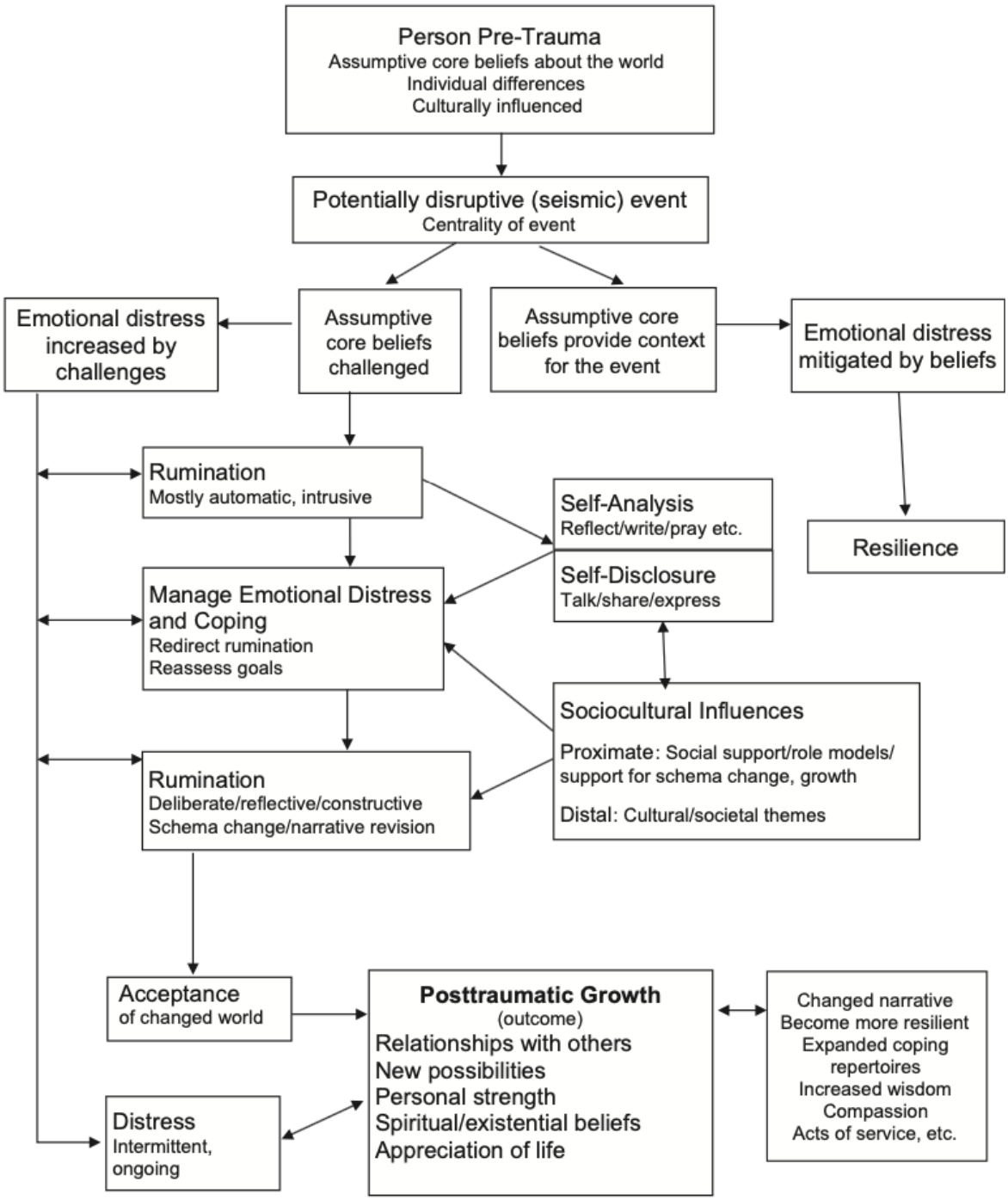


Fig. 1. *A revised model of Post-Traumatic growth*, taken from Tedeschi et al. (2018).

Other researchers have done significant work on models of PTG while building on the work of Tedeschi and Calhoun (1996). One such example is the **model of PTG and post-traumatic depreciation** (Taku et al., 2021). It emphasises that even though people may experience growth (e.g. appreciating how supportive others can be), they can also experience depreciation (e.g. perceiving others as uncaring). Notably, PTG and post-traumatic depreciation are not opposing

concepts, the two can co-exist in the same individuals. This is in line with findings around Post-traumatic Stress Disorder, which post-traumatic depreciation is associated with (Taku et al., 2021).

Another PTG model is the **Affective–Cognitive Processing** one (Joseph et al., 2012) which connects post-traumatic stress symptoms with PTG. Specifically, they describe that when the distress is very low or very high, PTG is not possible (U-shaped relationship). Regarding the former, it's because the world and the person's assumptions were not challenged enough and regarding the latter due to distress being debilitating and possibly leading to Post-traumatic Stress Disorder. At the same time, this model highlights the possibilities of people to move away from trauma and that growth is a normal result of successfully overcoming it.

A third model aiming to further elaborate the concept of PTG is the **Janus-Face model** (Maercker et al., 2004). It describes the need for short-term coping that allows for an increase in the self-enhancement cognitions (e.g. increased personal control) and a reduction in acute stress. This is in line with findings showing that PTG is associated with left frontal-brain activity which is more goal-oriented (Tedeschi et al., 2018). Moreover, the Janus-Face model notes that if such efforts are associated with avoidant coping (e.g. wishful thinking, naive optimism), it is likely the process turns into cognitive avoidance rather than PTG. However, their model is promoting the idea that people need, to a certain degree self-deceive to experience PTG, which can be perceived as disempowering or stigmatizing for some people.

Lastly, the **Cognitive Growth and Stress model** was shown to account for 30% of PTG in a diverse group of people (Brooks et al., 2017). The model highlights the importance of rumination, perceived control and centrality factors in the process of PTG. Regarding the latter, it concerns the centrality the event had around defining the self of the individual. Drawing from the ARC model (Boutillier et al., 2019), people with cancer experience both losses and changes in their identity. Therefore, cancer can be an identity-changing experience which in turn increases the likelihood of experiencing PTG.

Post-traumatic Growth in Cancer

According to a meta-analysis, PTG is sometimes reported in people affected by cancer (Marziliano et al., 2020). Narratives of people with cancer either in active treatment or remission include elements of PTG (Fioretti et al., 2020). The former concerned elements of incorporating cancer in their life trajectory, seek meaning and learning from cancer. The latter was described as close to PTG as defined in scientific literature, including elements of strength

and caring for one's self and others. These findings in both people in active treatment and remission are showing PTG for people in treatments for cancer is a process instead of a singular event with a clear start or conclusion.

Using the Common-Sense Model of illness representations (Leventhal et al., 1980) in people with cancer showed that low control, is a necessary but not sufficient condition to promote PTG in people with cancer and that it does not directly connect to PTG (Cao et al., 2018). This is suggesting the possibility of other mechanisms that connect the two that require further investigations. Additionally, higher social support predicted adaptive coping (e.g. active coping, planning, positive reframing), which in turn predicted PTG (Cao et al., 2018). This study is suggesting that a combination of internal processes (e.g. positive reframing) and external (e.g. social support) need to take place in order to best facilitate PTG in people with cancer.

According to a meta-analysis, PTG has been positively associated with health-related quality of life (QoL) (Liu et al., 2020) but also with **physical health outcomes** in people with cancer. For example, increased PTG was positively associated with improved recovery from chemotherapy (Dunigan et al., 2007). Meaning in life has been associated across studies and cultures with improved objective (e.g. biomarkers, survival) and subjective physical health (e.g. self-reports) in healthy individuals, people with cancer or other chronic illnesses (Czekierda et al., 2017). PTG has also been suggested to lead to health behaviours in people with cancer (Lim, 2019). Specifically, improvements in relating to others, new possibilities, appreciation of life, spiritual change and the total PTG score all predicted healthy eating and exercise levels. This could potentially offer a behavioural pathway to how PTG could improve outcomes of people with cancer.

According to a review, PTG has been negatively associated with depressive and anxiety symptoms and positively with hope, optimism, spirituality and meaning (Casellas-Grau et al., 2017). Regarding, **spirituality** and according to a review, a cancer diagnosis may lead the affected individual to question their fundamental assumptions and spiritual beliefs, sometimes resulting in deepening of such beliefs (Barata et al., 2016). PTG was predicted by the frequency of religious activities in people having undertaken hematopoietic stem cell transplantation (Jeon et al., 2015) and material attachment was a negative predictor of PTG in people with hematological cancers (Mousavi et al., 2020). These findings are suggesting a detachment from the material world and turning the focus toward spiritual elements, which could increase PTG and overall highlight the importance of spirituality in PTG for people with cancer.

A further area that has received attention in PTG for people with cancer is **meaning-making**, for example questioning the meaning in the life of the person with cancer (Barata et al., 2016). For example, a qualitative study with people with acute leukemia described a possible path towards building a renewed self, re-evaluating personal values and assigning new meaning to their experience (Papadopoulou et al., 2013). Specifically, following the initial blow of diagnosis, they were living in a contrasted world, having to deal with life in hospital, the several losses and the impact of their illness. Additionally, searching for meaning, focusing on benefits, self-reflecting and revaluating their thoughts and feelings helped them adapt better when they were in protective isolation (putting someone in an isolated room to decrease their risk of infection) (Biagioli et al., 2017). These findings are showing that meaning-making is important for people with cancer as it allows for increased PTG and helps them cope with some of the unique challenges of cancer.

Social support, information provision, coping style and hope were reported as beneficial to people with leukemia in the process of findings themselves again (Papadopoulou et al., 2013). PTG was predicted by support from healthcare professionals, social support, intrusive thinking and frequency of religious activities in people having undertaken hematopoietic stem cell transplantation (Jeon et al., 2015). Notably, social support provision is a dynamic process and sometimes social interactions may lead to conflict. Nevertheless, increased levels of social conflict in the present were associated with later increases in social support provision (Gerhart et al., 2018). This is suggesting that the social network is resilient and can readjust to better meet the needs of people with cancer. Therefore, improving access to social support shows promise for an intervention delivered by a professional to support people develop PTG.

All of the above seem to highlight different important areas in the field of PTG for people with cancer. Such areas can be targeted as part of an intervention aiming to improve PTG.

Interventions in PTG with people with cancer

Supporting the psychological needs of people with hematological cancers is considered the gold standard in oncological care and is believed to benefit their outcomes (National Institute for Health and Care Excellence, 2016). To achieve that, according to a meta-analysis of randomized control trials (RCTs) on PTG interventions for people with cancer, psychosocial interventions were effective in promoting PTG with mindfulness-based interventions being the

most common and effective (Li et al., 2020). Other effective PTG interventions targeted cognitive-based stress management and behaviour change. Notably, a social-support-only intervention was not effective.

One study could be retrieved that attempted to promote PTG and used a control group for people with hematological cancers. This non-randomized trial utilised a 22-week art intervention program and found no significant differences in PTG pre and post-intervention (Singer et al., 2012). This suggests that increasing PTG through art may not be sufficient to promote meaning-making or cognitive processing for people with hematological cancers.

Nevertheless, other studies found elements that support a PTG intervention in people with hematological cancers. A review concluded that meaning-making is a key part of adaptive coping and contributes to reducing physical, psychosocial and spiritual challenges and increasing personal growth and QoL (Adelstein et al., 2014). Discovering benefit seems to also be one of the most influential elements in research studies (Kou et al., 2021). Mental resilience was associated with PTG and could be successfully promoted in people with cancer (Ludolph et al., 2019). It was also suggested that interventions for people having undergone hematopoietic stem cell transplant should enhance support from professionals, counselling, self-help meetings and expressive writing (Jeon et al., 2015). On the other hand, PTG interventions in people with cancer have been criticized for being linear (Li et al., 2020), suggesting they do not allow for much flexibility or personalisation in their delivery therefore, there is a need for more non-linear and more dynamic PTG interventions.

BIOPSYCHOSOCIAL INTERACTIONS

Importantly, further to psychological growth, people's health includes complex biopsychosocial interactions. There is much research about these interactions in cancer (see Table 1, adapted from Cheng et al., 2019). For example, biomarkers like hemoglobin, c-creative protein (CRP) and albumin have been connected to cancer-related fatigue which can affect the QoL of the affected individuals (Saligan et al., 2015).

In particular, PTG was associated with a steeper diurnal cortisol slope which is suggesting a possible pathway between PTG, cortisol and cancer survival that needs further investigating (Diaz et al., 2014). The literature is also suggesting that the negative psychological effects of cancer may relate to the dysregulation of the Hypothalamic–Pituitary–Adrenal axis (HPA) (Diaz et al., 2014). However, this is a hypothesis that needs further investigating.

The majority of studies investigating biopsychosocial interactions in cancer are cross-sectional (Cheng et al., 2019), creating a need for more rigorous research designs. This need is also highlighted by the inconsistent associations sometimes found between different studies and cancer types (e.g. IL-6 in ovarian and lung cancers) and the need to control for mediation and moderation effects (e.g. symptoms of depression, fatigue) (Cheng et al., 2019).

Table 1. ***Association between psychosocial constructs and biomarkers***

Construct	Positive Associations	Negative Associations
Social support	Hemoglobin	
Positive mood/affect	C-creative protein (CRP), Hemoglobin, Albumin	
Coping style		Salivary cortisol slopes (flatter), CRP
Stress		Hemoglobin
Fatigue	C-creative protein (CRP)	Salivary cortisol slope (flatter)
Depressive symptoms / low mood		Salivary cortisol, Hemoglobin

Note*: Content adapted from Cheng et al. (2019).*

THE NOVELTY OF THE DOCTORAL PROPOSAL

Currently, according to the website https://clinicaltrials.gov, there are no ongoing interventions on PTG for people with hematological cancers. Therefore, this doctoral proposal will bring novelty in the field across five major axes: Research design, measurements, participants, intervention, recommendations.

Novelty in Research Design

Even though the overall conclusion is that there is a significant relationship between PTG and for example QoL, there is high heterogeneity in the findings. This is attributed to the

varying quality of the study designs (Tanyi et al., 2020). The presence of many cross-sectional studies without longitudinal measurements or control groups in PTG results in major methodological limitations, relating to the validity of the measurement, for example, the assessment of true PTG instead of short-term optimism (Jayawickreme et al., 2014). This raises the need for increased methodological vigour. The present proposal addresses these, by proposing an RCT, with repeated measures and a control group (see Design section). These will greatly contribute to increasing the reliability and overall generalizability of this doctoral project's findings.

Novelty in Measurements

Illness-related variables like, type of oncological treatment, cancer stage and severity of the stress are associated with PTG. However, few studies have investigated these in-depth or connected them with mechanisms and outcomes in people with cancer (Casellas-Grau et al., 2017). Similarly, variables like risk of recurrence and treatment traits (e.g. type, quality, efficacy) have been proposed to be studied further (Casellas-Grau et al., 2017). Moreover, in the Cognitive Growth and Stress model, perceived control seems to be closely related to PTG which is an element sometimes lacking in PTG research (Brooks et al., 2017). Therefore, this doctoral study will not only investigate illness perceptions around these but also clinical outcomes and biomarkers (see Measures section). It will also attempt to explain them using existing neurological pathways like the HPA axis (Diaz et al., 2014, Saligan et al., 2015).

Novelty in Participants

Research with people with cancer has been in the state of the art in the field of PTG in recent years (Kou et al., 2021). However, depside the high unmet needs of people with hematological cancers (Wang et al., 2018), they are rarely included in PTG research (Czekierda et al., 2017). This is especially important for PTG research as there are differences between the type of cancer and PTG which contributes to conflicting findings (Tanyi et al., 2020). Therefore, for this doctoral project, instead of having a blanket approach of including people with different types of cancer, only a targeted group of people with cancer will be approached, those with acute leukemia (see Participants section). The approach can then be adapted to facilitate delivery in different populations.

Novelty in Intervention

Overall, further evidence-based psychological interventions for people with hematological cancers are needed (Barata et al., 2016). Specifically underlined for PTG interventions is that further research is needed into the elements of different therapeutic interventions that would most effectively increase PTG (Joseph et al., 2012). At the same time, this is implicating emphasizing the need to draw from different therapeutic models to develop a PTG intervention. Moreover, having a manualised PTG intervention is especially important since PTG is conceptualized as rarely occurring intentionally by the affected individual (Tedeschi & Calhoun, 2004). Therefore, for this doctoral project, a tailored PTG intervention manual will be developed through the integration of multiple therapeutic elements (see Intervention section) for people with hematological cancers. Thus, instead of leaving people to experience PTG spontaneously, if at all, developing an intervention that prompts and accelerates PTG will empower people to actively experience growth, become more resilient and improve their QoL. In other words, a PTG intervention can not only help people overcome some of cancer's challenges, but also surpass cancer and gain things they did not have even before they were diagnosed.

Novelty in Recommendations

Lastly, this doctoral project aims to overcome barriers between clinical practice and research and better connect theory and practice by creating recommendations that are evidence-based and applicable to clinical practice (see Design section). This will allow for the latest evidence to inform clinical practice on a policy level and guide the psychosocial support of people with hematological and other cancer in oncological care. Such recommendations are considered especially important for the Greek health care system where this doctoral project will be conducted.

AIMS AND OBJECTIVES

The aim of this doctoral dissertation is designed to be implemented in two phases. Phase 1 aims to develop and evaluate the effectiveness of a PTG intervention manual for people with hematological cancers on biopsychosocial variables. Phase 2 aims to develop recommendations on how psychosocial interventions could be integrated into the Greek health care system. Its more specific objectives are:

Phase 1 – Post-traumatic growth intervention

i. Develop a post-traumatic growth intervention manual
ii. Investigate the feasibility of implementing the post-traumatic growth intervention in the Greek health care system
iii. Assess the effectiveness of a psychological intervention in increasing post-traumatic growth and other biopsychosocial variables in people with hematological cancers

Phase 2 –Policy Recommendations for the Greek health care system

i. Develop best practice guide on the psychosocial support of people with hematological malignancies in Greece
ii. Develop health policy recommendations on the integration of psychosocial interventions in oncological health care in Greece

METHODOLOGY

DESIGN

This is a non-pharmacological, interventional, repeated-measured, RCT study. It will develop and evaluate the effectiveness of a PTG intervention manual for people with hematological cancers on biopsychosocial variables and develop relevant recommendations (see Appendix A for Gantt Chart). Consultation from professional experts and experts by experience (e.g. people affected by cancer) will be sought at various points during the entire doctoral project (Phase 1 and Phase 2).

Phase 1 – Post-traumatic growth intervention

Initially, the PGT literature will be reviewed to select the appropriate definitions, theories, philosophical underpinning and other frameworks relevant to this doctoral dissertation. Furthermore, a **systematic review** of the literature will be conducted around the evidence-base of PTG interventions in cancer. The systematic review will follow recognised criteria, like PRISMA 2020 (Page et al., 2021) and the Cochrane Handbook (Higgins et al., 2019). It will not only include RCTs, but also predictors of PTG in cancer and account for the effectiveness of PTG interventions. The keywords could include:

- Leukemia OR leukaemia OR Cancer OR Oncology OR Stem cell transplantation OR bone marrow transplantation OR hematopoietic cell transplantation
- Posttraumatic growth OR post-traumatic growth
- Intervention OR predictor OR mediator OR moderator

The databases and journals that could be reviewed:

- PubMed
- Science Direct
- Wiley Online Library
- Taylor & Francis Online
- Psycho-Oncology
- Journal of Psychosocial Oncology
- European Journal of Cancer Care
- Journal of Loss Trauma
- Psychological Trauma Theory Research Practice
- Journal of Traumatic Stress

To reduce publication bias, the review will not be limited by the year of publication and reasonable effort will be put in retrieving non-published works (e.g. PhD or Masters dissertations).

The conclusions of reviewing the literature will help develop the initial draft of the **intervention manual**. The manual will then be shared for comments with experts in the field of PTG (e.g. Tedeschi, Calhoun, Romeo, Li), expert medical groups (e.g. European Leukemia Network, European Hematology Association, Hellenic Society of Hematology) and expert patient groups (e.g., Greek Federation of Cancer - ELLOK). Their comments will be reviewed and changes to the manual will be made appropriately.

After the intervention manual has been reviewed, a **pilot study** will be conducted for an initial evaluation of the developed intervention and the feasibility of conducting such an intervention in the Greek health care system. Specifically, a small number of eligible participants (see Participants' section) will be contacted to participate. There will be no control group for the pilot. The pilot will allow the research team to gain experience with the implementation of the intervention and gain insights into how it could be improved on. Formal feedback (e.g. interviews, focus groups) will be sought from the participants of the pilot group as to how the intervention and its processes could be improved. Specifically, the lessons learned and feedback for the pilot study will lead to the final amendments of the intervention manual and overall how the intervention is implemented (e.g. group or individual setting).

The **RCT** will then be undertaken to further evaluate the effectiveness of the intervention, including its generalizability and applicability to a large group of people. The control arm of the trial will receive usual care and no intervention. Due to the nature of the intervention, it will be a non-blind RCT. Feedback from the participants of the intervention will be sought. Quality manuals and criteria for RCTs will be used; these include the Cochrane risk-of-bias tool (Higgins et al., 2011) and the Delphi List on quality assessment of RCTs (Verhagen et al., 1998).

Phase 2 – Policy Recommendations for the Greek health care system

Findings from the feasibility pilot and the RCT, including the feedback from the participants, as appropriate, will contribute to the development of a **best practice guide** on the psychosocial support of people with hematological malignancies in Greece. These will be developed from findings, reports and observations from having undertaken the present doctoral project. They could present, the needs of people with hematological cancers and common practices in developed countries. For example, a review of interactional best practice recommendations in the field will be consulted (e.g. The National Institute for Health and Care

Excellence), culturally adapted for Greece and appropriately integrated into the Greek health care system to generate clinically applicable best practice recommendations.

Findings from the literature review and from the overall experience of conducting the present study will contribute to the development of **health policy recommendations** on the integration of psychosocial interventions in oncological health care in Greece. These will include, identifying difficulties and barriers, what policy actions could address these, how to provide psychosocial support in this context and what the impact of implementing such a policy could have. The goal is to develop a health policy that is evidence-based and realistically applicable to the Greek health care system.

PARTICIPANTS

A priori power calculations will be conducted using G*Power 3 (Faul et al., 2007) to estimate the number of participants needed and to minimize the likelihood of type 1 and 2 errors: finding false positives or not finding an effect when one exists (Robson & McCartan, 2016). Thus, avoid overrecruiting. It is currently estimated that around 40 participants for each arm of the RCT should be sufficient (n = 80).

Purposive recruitment (Robson & McCartan, 2016) will be employed to recruit participants. Recruiting from medical systems has been recommended in previous PTG research with people with cancer (Teh, 2018). Therefore, participants will be recruited across major hematological centers in Greece (indicatively, Papanikolaou and AHEPA hospitals) through an existing network of collaborators of the Center of Research and Technology Hellas (CERTH).

Participants will be allocated randomly to the intervention or control group according to a specialised software developed in the CERTH. The researcher will not influence this outcome. The following inclusion and exclusion criteria will be used which are in line with previous research projects (see Table 2).

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion
1. Adults (≥ 18 years) 2. Having a diagnosis of a. Acute Lymphoblastic Leukemia (ALL) or	1. Being in active psychological or psychiatric treatment 2. Having an unmanaged mental health difficulty

b. Acute Myeloid Leukemia (AML) or c. having undergone allogeneic hematopoietic cell transplantation. 3. Having concluded the planned chemotherapy courses and related hospital admissions 4. Having no more than 5 years since the initial diagnosis.	3. Having a severe cognitive impairment 4. Being unable to give informed consent 5. Being unable to speak or read Greek 6. Having one or more relapses 7. Diagnosed with another type of cancer within 5 years prior to recruitment. 8. Having less than one-year life expectancy

If the recruitment process does not result in sufficient power, then further efforts will be put to increase the recruitment rate (e.g. recruiting from further hospitals affiliated with CERTH). If there is still an insufficient number of participants within a year, then the analysis will only include those already participating. New ad hoc compromise power calculations will be conducted to calculate the power with the existing numbers (Faul et al., 2007) and instead provide findings for a feasibility, pilot RCT.

PROCESS

Recruitment will be conducted through major hematological centers (indicatively, Papanikolaou and AHEPA hospitals). Healthcare professionals working with patients in these centers will inform them of the study and should they wish further information, the healthcare professionals will share the participants' names and contact details with the researcher (see Ethical Considerations section). The researcher will then contact the prospective participants and arrange a time to gain informed consent. Once this is secured, the participants will complete the pre-intervention outcome measures. Participants will also be given the necessary home-kits to measure their saliva cortisol levels at pre-specified times (see Measures section). Written details around how to use these and relevant training will be offered to all participants with the first measurement taking place in the consent meeting. The random allocation of the participants to either the control group or the intervention group will take place. The participants will be informed of their allocation status along with details of what that entails. The participants will be contacted 24 hours after they have consented to reaffirm their participation in the study.

The intervention will be designed to accommodate both individual (1-1) and group settings (6-8 people, one facilitator). Support from peers with similar experiences has been recommended in facilitating PTG (Tedeschi & Calhoun, 2004), potentially increasing the

intervention's effectiveness. Additionally, group interventions can be more time-efficient. Therefore, for this study and adopting to possible COVID-19 restrictions at the time, a group setting will be initially implemented and evaluated in the pilot. According to the feedback of the participants of the pilot, the group setting will either be adopted for the RCT or it will be amended into the individual setting.

Once a sufficient number of participants is reached, the group will be formed and the intervention will commence at an agreed and convenient time and date to all participants. Possible facilitation locations for these meetings are at the participating hospitals, at CERTH or at the premises of a patient advocacy group. In the first meeting of the intervention, the goals and overview of the intervention will be presented. Following the completion of the intervention, the outcome measures will be administered once again to both groups. The participants will also be approached again at 3 and 6 months following the conclusion of the intervention to complete the outcome measures (see Measures section). Both groups will be offered the option to either complete the measures in person or via a telephone interview with the researcher.

Six months after the end of the intervention, the clinicians facilitating the recruitment will be contacted by the researcher to share the relevant biomarkers from the person's file. Only the specified biomarkers (see Measures section) and only for the specified time-points (pre, post-intervention, 3 months and 6 months post) will be shared with the researcher.

INTERVENTION

The intervention will be delivered by the researcher (Health Psychologist), it will last 8 weeks (Li et al., 2020), and it will be of medium intensity (90mins weekly sessions; Ludolph et al., 2019) as it is common in effective PTG interventions in people with cancer. This intervention will be dynamic and tailored to the individuals receiving it. Since many PTG interventions have been limited by being linear (Li et al., 2020), this intervention aims to allow people to move across the different domains of the manual according to their preferences. This will also allow for better tailoring of the intervention to the participants' preferences which will lead to more person-centered intervention. Not every person is the same or experiences the same things, therefore, such tailoring is needed. In practice, this would mean moving between the different domains of the intervention manual or omitting some according to the present needs and preferences of the individuals receiving the intervention. This will also allow spending more time on a given component if relevant.

To effectively address the domains of PTG, this intervention will be multi-faceted, theory-driven and evidence-based. For example, since cognitive processing in PTG has been emphasised (Tedeschi & Calhoun, 2004), this intervention will aim to facilitate such cognitive processes. Similarly, since PGT interventions in people with cancer aiming to improve resilience were found to be effective when having elements of CBT (Ludolph et al., 2019) and since mindfulness is effective in promoting PTG in people with cancer (Li et al., 2020), both will be unutilised appropriately. Unconditional positive regard is considered to be important for this intervention. Furthermore, the intervention will draw from PTG models and research including:

- The model of Tedeschi et al. (2018) on the process of PTG (also see Calhoun & Tedeschi, 1998; 1999, Tedeschi & Calhoun, 2004)
- The Cognitive Growth and Stress model (Brooks et al., 2017)
- The Affective–Cognitive Processing (Joseph et al., 2012)
- The model of PTG and post-traumatic depreciation (Taku et al., 2021)
- The Janus-Face model (Maercker et al., 2004)
- The work of Berger et al. (2009) on the role of the family in PTG
- The work of Tedeschi and Moore (2020) on PTG as an integrative therapeutic philosophy.

Some examples of the paradigms and elements of the intervention outside of the PTG field the intervention will be drawing from are:

- CBT: Psychoeducation on trauma, relaxation techniques training (e.g. mindfulness) and challenging of core beliefs.
- Narrative: Chronological narrative of one's life, review of past traumatic and positive life events and expressive writing.
- Existential: Meaning and purpose-finding, including questions of fairness and justice.
- Interpersonal: Expanding their social support networks and identifying those individuals most suited to support them.

MEASURES

Several measures will be used to assess the effectiveness of the intervention. These will be collected at four time points: pre and post-intervention and at 3 and 6 months following the conclusion of the intervention. To reduce the likelihood of positive response bias sometimes found in PTG research (Jayawickreme et al., 2014), measurements of both negative and

positive constructs will be undertaken. Some of the main measures that will be used are presented below.

Particular emphasis will be put on **demographics** (e.g. gender, age) and clinical characteristics (e.g. diagnosis, time since treatment), to investigate whether these tend to predict the outcome of the PTG intervention, as the literature is suggesting. For example, age (Jones et al., 2015), gender (Tedeschi & Calhoun, 2004) and diagnosis (Li et al., 2020), all seem to be connected directly or indirectly with PTG.

Information on specific **biomarkers** will be collected as outcomes. They are selected due to their potential to be affected by this psychosocial intervention (Cheng et al., 2019) and the possibility to improve the overall outcomes of the participants, including survival, through the HPA axis (Diaz et al., 2014). They will be a means to investigate the impact of the intervention on biological and clinically relevant markers. Specifically, the clinicians will share with the researcher the measurements on hemoglobin, c-creative protein (CRP) and albumin from the medical file of the participants (see Ethical Considerations section). The participants will not be required to undertake any further testing for these biomarkers outside of their routine monitoring. An additional biomarker that has also been selected is that of cortisol slop measurement. It will be measured using a home kit (e.g. Verisana) by the participants after appropriate training (see Process section). These will be procured and distributed to the participants for this purpose. The results will be posted using pre-paid postage to CERTH where they will be analysed.

Post-traumatic Growth Inventory (PTGI; Tedeschi & Calhoun, 2004), will be the **primary outcome**. PTGI is the most commonly used measure in RCTs of PTG interventions for people with cancer (Li et al., 2020). It is a 21-item on a 6-point Likert scale theory-driven questionnaire, where higher scores indicate higher PTG. The scale has been tested against and was found not to correlate with the bias of social desirability. Additionally, PTGI, in line with the PTG theory, was found to detect higher benefit on people who have experienced traumatic events than those who have not experienced such events (Li et al., 2020). The latter suggests good construct validity. A Greek version of the PTGI has been developed using a standard back-translation process with a group of people receiving palliative care for advanced cancer (Mystakidou et al., 2008). Five constructs of PTG are included in the Greek version: confrontation, relating to others, new possibilities, appreciation of life, and spiritual change. Cronbach's alphas for the five factors were good and ranged from 0.66 to 0.87, test-retest reliability was satisfactory with a range between 0.85 and 0.92 ($p < 0.01$), and inter-item

correlations ranged between 0.47 and 0.63. Appropriate approval for use will be secured by the researcher from all relevant parties.

According to a review (Raphael et al., 2017), the **Impact of Event Scale - Revised** (IES-R; Weiss, 2007) is commonly used to measure subjective distress caused by a traumatic event in hematological cancer survivors. The perceived impact of the traumatic event may influence the degree of PTG (Tedeschi & Calhoun, 2004). The IES-R is a validated 22-item measure of an individual's response to a specific trauma (Beck et al., 2008). IES-R measures the impact of the trauma on the last 7 days using a 5-item Likert scale. Higher scores indicate higher impact. It measures three subscales: Avoidance, Intrusion and Hyperarousal. The IES-R has been previously translated in Greek and has been found to have good Cronbach's alpha (ranging from 0.72 to 0.85) and good test-retest ($p < 0.01$; Mystakidou et al., 2007). Appropriate approval for use will be secured by the researcher from all relevant parties.

The **Brief Illness Perceptions Questionnaire** (BIPQ, Broadbent et al., 2006) is composed of eight closed questions rated on a 10-point Likert scale, and one open question ("*Please list in rank-order the three most important factors that you believe caused your illness*"). The items tap into categories of illness perceptions which are assessed differently. Higher scores on consequences, timeline, identity and emotional response indicate a higher perceived severity, which was shown to predict PTG (Ponto et al., 2010). Higher scores on personal and treatment control and illness coherence, indicate more positive illness perceptions and higher perceived control over the illness and have been proposed for further study (Casellas-Grau et al., 2017). From that, when calculating the total score, reverse scoring is required. The BIPQ is a reliable, theory-driven questionnaire (Broadbent et al., 2006) with good test-retest reliability for most scales in two time-points ($p < 0.01$) and good concurrent validity with significant correlations with the Illness Perceptions Questionnaire - Revised-R items for each scale ($p < 0.01$). BIPQ has been translated into Greek (Hyphantis et al., 2013). Appropriate approval for use will be secured by the researcher from all relevant parties.

The **World Assumptions Scale** (WAS; Janoff-Bulman, 1989) will be used to measure assumptions about the benevolence of the world using 32 items on a 6-point Likert scale. Subscales include the benevolence of the impersonal world, the benevolence of people, randomness, justice, controllability, self-worth, self-control, and luck. The reliability of these eight subscales of the WAS range from 0.48 to 0.82 (Elklit et al., 2007). Such assumptions about the world seem to be connected to PTG through the perceived nature of the traumatic event (Tedeschi & Calhoun, 2004). WAS has been translated into Greek (Tešanović, 2018). Appropriate approval for use will be secured by the researcher from all relevant parties.

The **Hospital Anxiety and Depression Scale** (HADS; Zigmond & Snaith, 1983) can be used to measure anxiety and depression with a higher score indicating higher mental health difficulties. It is a 14-item scale, using a 4-point Likert scale and has been widely used in research with people with cancer (Wang et al., 2018). HADS has been translated in Greek and validated for people with cancer (Mystakidou et al., 2004) and has good Cronbach's alphas for both the anxiety and depression scales of 0.89 and 0.70, respectively. Appropriate approval for use will be secured by the researcher from all relevant parties.

The **Functional Assessment of Chronic Illness Therapy—Spiritual Well-being** version 4 (FACIT-Sp) is a 39-item measure of QoL and well-being that uses 5-point Likert scales (Peterman et al., 2002). It has the following well-being scales: Physical, social/family, emotional, functional and spiritual. Accounting for reverse scoring, higher scores indicate better QoL and well-being. FACIT-Sp is frequently used as a measure of QoL with people with cancer in PTG research (Czekierda et al., 2017). FACIT-Sp has been translated in Greek (FACIT Group, n.d.), it validand reliable (Cronbach's alpha between 0.81 and 0.88) for people with cancer (Peterman et al., 2002). Appropriate approval for use will be secured by the researcher from all relevant parties.

ANALYSES

All the statistical analyses will be conducted using SPSS 23. Data screening will include identifying and dealing with outliers and testing the assumptions for the tests used. To meet the relative aims and the objectives, among other analyses, a series of Pearson or Spearman correlations will be conducted between the items measured. A number of *t*-tests will be conducted to evaluate the effectiveness of the intervention by comparing the mean scores of the control and the intervention groups. To investigate further differences between the groups (e.g. biomarkers), *t*-tests, ANOVA and χ^2 will also be used appropriately. Moreover, regression analysis (e.g. linear, logistic, multivariable) will be performed to assess the degree any pre-intervention measurements predicted the outcome of the intervention. If there is sufficient power, structural equation modelling could also be used to investigate the relationships between the variables and PTG with the view to develop a model based on the findings for PTG and people with hematological cancers.

At the same time, the included questionnaires will be analysed using Cronbach's alpha to ensure they are valid in this specific population. Similarly, factor analysis will allow to explore how well the original five domains of PTG (Tedeschi & Calhoun, 1996) and those developed for the Greek PTGI (Mystakidou et al., 2008) fit this population.

Feedback from participants (e.g. pilot) will be sought during the development and the evaluation of the PTG manual using interviews of focus groups as appropriate. Similarly, after the RCT, participants with the highest score changes, those with the highest or lowest PTG could be approached for feedback and to share their experiences. These will be recorded, transcribed and analysed thematically (Braun & Clarke, 2006).

ETHICAL CONSIDERATIONS

The present study will take place after gaining ethical approval from the respective ethics committees of a. the University of West Attica, b. CERTH and c. each participating hospital.

All sensitive information will be stored according to the EU General Data Protection Regulation (GDPR) (Voigt & Von dem Bussche, 2017). CERTH is ISO certified in GDPR. The researcher will have access to the data and will allow others (e.g. supervisors) to access this data if they have a legitimate reason to do so. No one outside the research team will have access to the data. Password-protected and securely stored computers will be used. Any information that could identify the participants will be anonymized and participants will be given an ID code. Only one password-protected document will connect the participant's details and their ID code. Anonymity will be maintained at all stages of the dissemination process.

During the recruitment process, participants will be informed about the nature and purpose of the study in writing (information sheet); including the protection of their confidentiality and anonymity, of their right to refuse to answer questions or to remove themselves from the study for any reason and at any time before the final anonymization of the data . Participation will be voluntary and no momentary motivation will be offered. Participants will be reassured that their decision to participate or withdraw will not affect their care in any way. Following their agreement with the above, they will be recruited into the study by signing a consent form. The participants will further be asked to confirm their consent 24 hours after the consent meeting. If any participant shares they want to withdraw from the study, any information will be removed from the records (e.g. completed questionnaires, clinical and demographic information) and any biomarker samples shared will be securely destroyed. Participants will be offered the opportunity to receive a copy of the results in writing in a non-academic language and engage in discussion with the researcher should they wish.

Regarding the biomarkers' collection, the researcher will not have access to the participants medical record. The clinician will share the relevant information securely and according to GDPR procedures with the researcher. The consent form will specify offering

consent to share each of the biomarkers individually. Details for the nature of each biomarker will be given on the information sheet.

Concerning the cortisol measurement, it is considered minimally invasive as it is drawing a sample from saliva (instead of urine or blood). The kits are specifically designed to be undertaken by non-professional in a home setting. This reduces the burden of travel and the related risk of infection due to an additional hospital visit. Participants will be offered in-person support in undertaking this procedure and instructions in writing during the consent process. Over-the-phone, support will be offered as needed. The results will be sent using pre-paid and pre-coded postage so the participants do not have to pay the costs involved. The code will protect the anonymity of the participants and ensure that only the researcher can make the connection between the parcel and the participant's ID.

The research will not involve physical, legal or social risks beyond those normally encountered by the participants in their life outside research. However, regarding the psychological dimension, some of the purposed measures include sensitive questions (e.g. emotional distress, QoL) and participants may be asked to talk about difficult topics (e.g. their diagnosis), these could also lead to some initial distress. To mediate this, people who are in acute treatment will not be approached. Furthermore, to help them manage distress, coping strategies (e.g. mindfulness) will be delivered to individuals as part of the intervention. Additionally, the contact information of the researcher (Health Psychology M.Sc., male) will be provided to all participants in the information sheet to offer the option of further support with any difficulties arising from their participation in this study. The researcher has previous experience interviewing and offering support to vulnerable individuals. Additionally, no one will be made to discuss anything they do not feel comfortable with. The participants will also be provided with a debrief sheet at the end of their participation or as needed, providing further information about a range of helpful sources.

Any issues found in the course of the study around the safety of the individual or others will be addressed as a priority over the individuals' participation in the study. Any such issues will be raised with the individual directly and access to support will be facilitated.

IMPLICATIONS AND DISSEMINATION

This will be the first RCT in PTG intervention for people with hematological cancers and the only second control trial on this topic. Therefore, it will contribute to the available evidence-based interventions for people with hematological cancers. This intervention will help them not only cope better with cancer but also grow as a result. This intervention holds

the potential to improve their PTG, QoL, wellbeing and to decrease their anxiety, depression, and distress. It also holds the potential to improve people's health outcomes and thus decrease health-related costs and possibly improve their long-term survival.

Developing an intervention manual and making it available to both the research and clinical community, will accommodate further evaluation by future studies. Through the Open Science approach, the findings will be communicated and disseminated with experts in the field that could further the evidence-base of the intervention. Should its validity be proven across populations and countries, then it could be implemented by healthcare professionals supporting people with hematological cancers.

The results (findings and generated recommendations) will be offered to the participants and presented to the health care professionals and clinical centers involved in the recruitment process. The results will also be shared with patients' (e.g. Greek Federation of Cancer - ELLOK) and healthcare professionals' societies in Greece (e.g. Hellenic Society of Hematology). Similarly, the results will be offered to experts in the field of PTG (e.g. Tedeschi, Calhoun, Romeo, Li) and expert medical groups (e.g. European Leukemia Network, European Hematology Association, Hellenic Society of Hematology). An opportunity to discuss the results with the researcher will also be pursued with all of them.

At the same time, as part of the dissemination process, a dedicated website can provide details around the intervention, publications, the intervention manual and recommendations. The traffic of the website will be monitored to assess the impact of the intervention. The following major publications could be produced by this doctoral dissertation:

1. A Systematic Review of PTG interventions for people with cancer.
2. A manualised PTG intervention for people with hematological cancer.
3. A pilot study on a novel, integrated, PTG intervention for people with hematological cancer.
4. An RCT on a novel, integrated, PTG intervention for people with hematological cancer.
5. Best practice and policy recommendations for psychosocial support in oncological care in Greece.

According to a review of the term PTG (Kou et al., 2021), the following journals have published most of the articles relating to the PTG some of which are oncological journals:

1. Psycho-Oncology (106 publications),
2. Journal of Loss Trauma (95 publications),
3. Psychological Trauma Theory Research Practice (68 publications),

4. Journal of Traumatic Stress (54 publications)
5. Journal of Psychological Oncology (41 publications)

Therefore, the above journals will be considered for the major publications arising from this research.

The findings will also be submitted in conferences such as the European Hematology Association Congress, International Conference on Hematology and Oncology, The Annual Hellenic Hematology Congress, European Health Psychology Society Conference and the British Psychological Society - Division of Health Psychology Conference.

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APPENDIX A – GANTT CHART

		Y1			Y2			Y3			Y4		
		M1-4	M5-8	M9-12	M13-16	M17-20	M21-24	M25-28	M29-32	M33-36	M37-40	M41-45	M45-48
Phase 1: Post-traumatic growth intervention	Review the PTG literature and adopt definitions, theoretical and philosophical underpinnings												
	Systematic review of the PTG literature in cancer, emphasising on interventions												
	Develop the intervention manual												
	Finalise the manual by consulting with professional experts and experts by experience												
	Ethics												
	Conduct a pilot study												
	Seek feedback from participants												
	Conduct an RCT to investigate the effectiveness of a psychological intervention in increasing post-traumatic growth in people with hematological cancers												
	Seek feedback from participants												
	Analysis												
Phase 2: Policy Recommendations for the Greek health care system	Develop best practice guide on the psychosocial support of people with hematological malignancies in Greece												
	Develop health policy recommendations on the integration of psychosocial interventions in oncological health care in Greece												
Writing & Dissemination	Introduction												
	Methods												
	Findings												
	Conclutions												
	Publications			Review	Manual		Pilot			Recom.	RCT		