DOCTORAL THESIS

# Developments to established dose-finding methodologies for application in trials with complex and innovative designs


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# *Abstract*

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by Amit PATEL

Insert abstract here...

# *Acknowledgements*

Acknowledge people here . . .

# Contents

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# Chapter 1

# Implementing the PO-TITE-CRM trial design into ADePT-DDR

## 1.1 Draft Structure

- Introduction
  - Basic biological background
  - Main objective of the trial
  - Introduce the new TD notation link to previous trial designs
  - Paragraph on traditional dose finding trial designs 3+3, CRM etc.
  - Methodological issues which arise due to investigating combination of drugs/varying parameters (new concept by Piers)
  - Necessity of time-to-event components for DLTs which may occur later
  - Other possible methodologies in this area which may be of use to solve this problem
  - Mini literature search will do a citation search for both methodology papers (potentially use a table/figure to summarise)
  - Detail whats to come in the chapter

- The PO-TITE-CRM Design
- PO-TITE-CRM in ADePT-DDR
- Modifications to the specification to improve operating characteristics

## 1.2 Introduction

Worldwide there are approximately 600,000 new cases of Head and Neck Squamous Cell Carcinoma (HNSCC) each year [1]. Of which, 12,000 occur in the UK with the most common forms of treatment being surgery, radiotherapy and/or [2]. Radiotherapy is essential for the treatment of cancer, it has been estimated that more than 40% of patients will receive radiotherapy at some point in their treatment [3]. However, despite recent advancements in radiation techniques and the use of of concomitant chemo radiotherapy, patients with solid tumours such as head and neck cancer have suboptimal cure rates [2], [4]. For those with advance HNSCC primary radiotherapy with concurrent chemotherapy is often offered but, it has not been shown to improve survival in patients aged over 70 compared to radiotherapy alone [5]. Therefore, any strategy to improve the efficacy of radiotherapy without increasing toxicity to normal tissue would have a significant impact for patients. DNA damage repair (DDR) inhibition is a potential technique which could be utilised as it potentiates the therapeutic effects of ionising radiation in cancer cells without a substantial increase in acute and late toxicity. Combining radiotherapy with DDR inhibition could improve clinical outcomes for these patients [6].

### 1.2.1 Subsection 1

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## 1.3 Main Section 2

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# Appendix A

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