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# Optimizing drug development of anti-cancer drugs in children using modelling and simulation

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Modelling and simulation (M&S)-based approaches have been proposed to support paediatric drug development in order to design and analyze clinical studies efficiently. Development of anti-cancer drugs in the paediatric population is particularly challenging due to ethical and practical constraints. We aimed to review the application of M&S in the development of anti-cancer drugs in the paediatric population, and to identify where M&S-based approaches could provide additional support in paediatric drug development of anti-cancer drugs. A structured literature search on PubMed was performed. The majority of identified M&S-based studies aimed to use population PK modelling approaches to identify determinants of inter-individual variability, in order to optimize dosing regimens and to develop therapeutic drug monitoring strategies. Prospective applications of M&S approaches for PK-bridging studies have scarcely been reported for paediatric oncology. Based on recent developments of M&S in drug development there are several opportunities where M&S could support more informative bridging between children and adults, and increase efficiency of the design and analysis of paediatric clinical trials, which should ultimately lead to further optimization of drug treatment strategies in this population.

## Introduction

Drug treatment in the paediatric population is still frequently off-label, with dosing regimens commonly empirically derived from adult clinical trial data [1]. However, changes in physiology during paediatric development may have substantial impact on drug pharmacokinetics (PK) and pharmacodynamics (PD) [2]. A recent review of paediatric drug studies showed that for a substantial number of evaluated drugs, adjustments in dosing regimens and formulations were necessary [3]. In paediatric oncology, the conduct of prospective drug development studies has been relatively limited as well, resulting in higher percentages of off-label use in this therapeutic area [4, 5]. For instance, single agent phase I studies have only been conducted to a very limited extent [6]. Study designs in paediatric oncology commonly evaluate safety and efficacy of anti-cancer agents by adding the treatment to existing regimens, which potentially leads to complex combination treatments that are difficult to evaluate. Practical limitations such as obtaining (additional) blood samples, and the low number of patients that are typically available for participation in clinical studies [7] further complicate the conduct of drug development studies. Thus, the need for informative and efficient clinical study designs in this particular patient population is of special relevance.

The need for improved pharmacotherapy in children and associated drug studies has also been recognized and encouraged by regulatory bodies through a number of programmes and guidelines [8, 9]. The FDA has provided a paediatric study decision tree to help assessment of clinical studies that are necessary during paediatric drug development [10] (Figure 1). Based on this decision tree, three basic study types are distinguished: (i) PK bridging studies, (ii) exposure–response studies and (iii) studies evaluating safety and efficacy, to which we will refer to as a full drug development study. In addition to the studies in the FDA

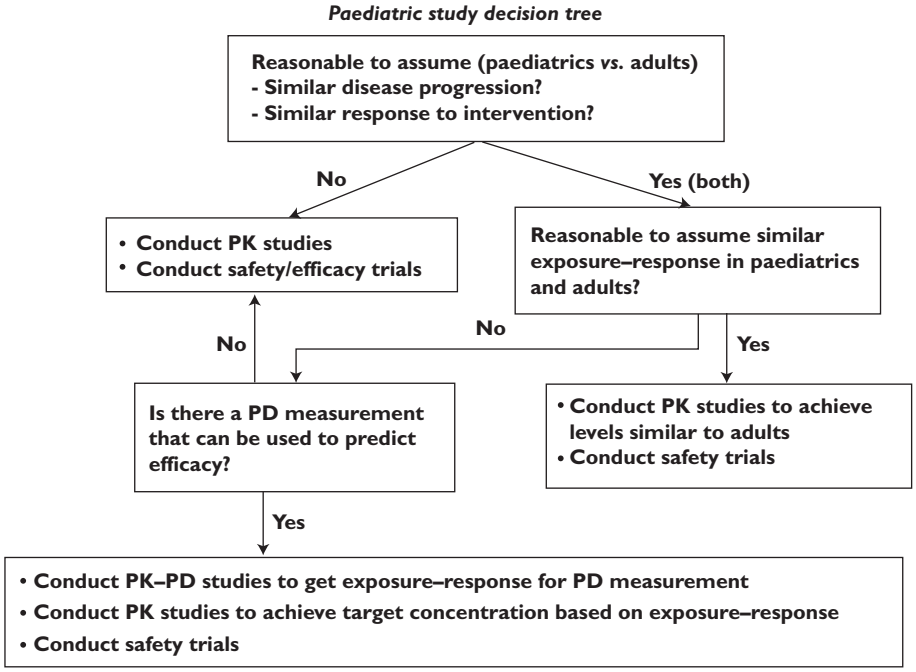


**Figure 1**

Paediatric decision tree to determine necessary paediatric clinical studies, as suggested by the FDAPK, pharmcokinetic; PD, pharmacodynamic

decision tree, studies aiming to perform *post hoc* drug-treatment optimization of toxicity or efficacy can also be distinguished. The current review is centered around these four types of studies.

Paediatric PK bridging studies aim to determine dosing regimens that will lead to target exposures similar to adults. However, if differences in disease progression or the exposure–response relationship are expected, bridging cannot be based solely on adult target exposure levels. Differences in disease progression can be common in paediatric oncology, and are related to the differences in biology of paediatric malignancies, compared with adults (e.g. sarcoma *vs*. carcinoma) [11], which also lead to differences in response rate [12]. In such cases, the FDA guidelines recommend either an exposure–response study, using surrogate biomarkers predictive of efficacy, or alternatively a full evaluation of safety and efficacy, e.g. a full drug development study.

Drug treatment optimization studies typically aim to identify either (i) patient characteristics predictive of (some of the) inter-individual variability in drug exposure, (ii) develop therapeutic drug monitoring and/or limited sampling strategies or (iii) investigate potential drug–drug interactions.

Modelling and simulation (M&S) in clinical pharmacology and drug development may be roughly defined as the area which involves development and application of mathematical and statistical models which describe PK and PD. Regulatory authorities have suggested that M&S based approaches may be used to support the development of dosing regimens in children [13–16]. Several review articles have been published which discuss and demonstrate the potential value of M&S to support design and analysis of paediatric drug studies and associated decision making [17–20]. An overview of the role of M&S in (paediatric) drug development is depicted in Figure 2.

The overall objective of this review was to review systematically the literature for publications that applied M&S to support the development of anti-cancer drugs in the paediatric population. In this review, we will discuss identified analyses in the context of the earlier described four study types that are relevant to paediatric drug development: (i) PK bridging studies, (ii) exposure–response studies, (iii) full drug development studies and (iv) drug-treatment optimization studies. Additionally we aimed to identify and discuss M&S-based approaches that could potentially address some of the challenges associated with the design and analysis of paediatric drug development studies of anti-cancer drugs.

## Methods

A systematic search on PubMed was performed in which search terms were chosen to identify publications where

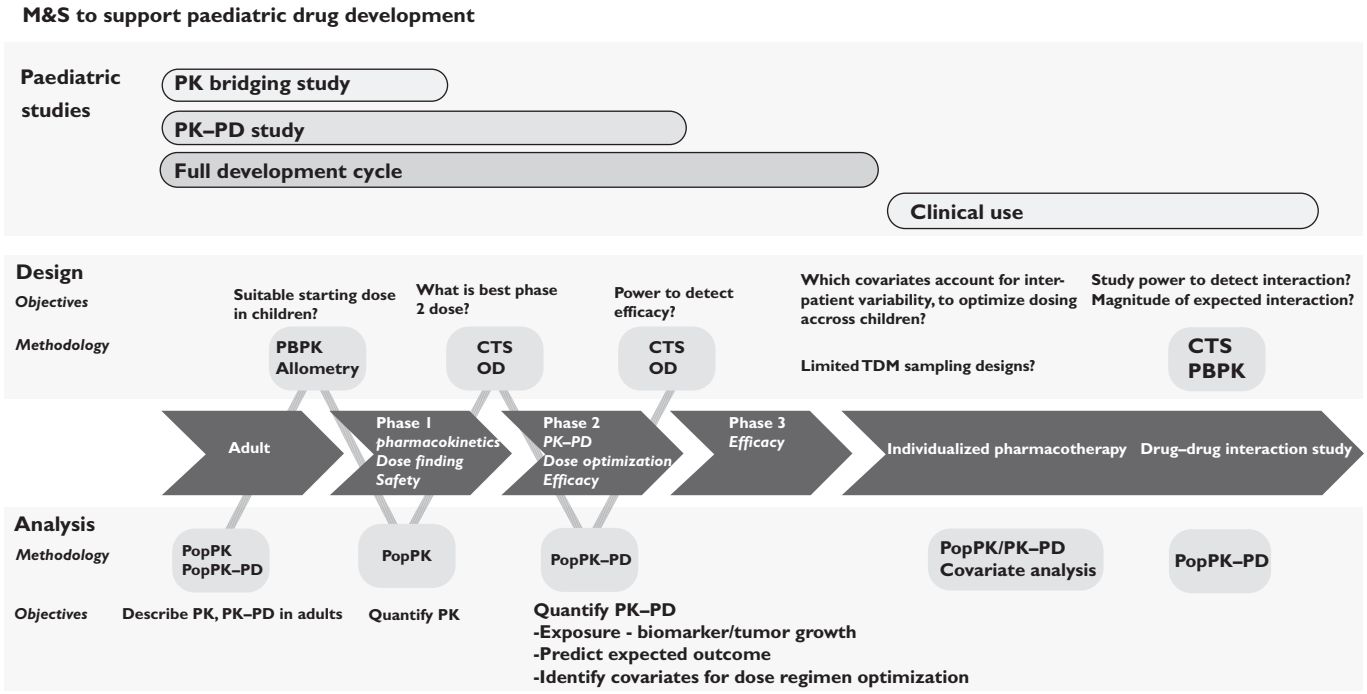


**Figure 2**

Schematic overview of the role of modelling and simulation (M&S) in paediatric drug development. CTS, clinical trial simulation; OD, optimal design; PK–PD, pharmacokinetic–pharmacodynamic modelling; PBPK, physiologically-based pharmacokinetic modelling

M&S were used to support development of anti-cancer drugs in the paediatric population. The search query consisted of five components addressing: (i) keywords for different possible types of M&S based analyses, (ii) keywords for different possible software packages, (iii) keywords indicating a paediatric study population and (iv) keywords indicating anticancer drugs were investigated. Additionally, with respect to this last component, we added a number of frequently used anti-cancer drugs also specifically.

The specific search query used was as follows: ('population pharmacokinetic*' OR 'PK–PD model' OR 'pharmacokinetic model' OR 'pharmacodynamic model' OR 'NONMEM' OR 'PBPK' OR 'Physiologically-based model*' OR 'physiology-based model*' OR 'non-linear mixed effect' OR 'WinNonMix' OR '*bugs' OR 'S-ADAPT' OR 'monolix' OR 'PK-Sim' OR 'Simcyp') AND ('paediatric'[TIAB] OR 'paediatric' OR 'childhood'[TIAB] OR 'paediatric'[TIAB] OR 'children'[TIAB] OR 'neonates'[TIAB] OR 'toddlers'[TIAB] OR 'adolescent'[TIAB]) AND ('cancer'[TIAB] OR 'oncology'[TIAB] OR 'malignant*'[TIAB] OR 'Leukemia' OR 'anticancer' OR 'anti-cancer' OR 'chemotherapy' OR 'neoplasms' OR '*neoplastic*' OR 'etoposide'[TIAB] OR 'methotrexate'[TIAB] OR 'MTX' OR OR 'actinomycin D'[TIAB] OR 'asparaginase'[TIAB] OR 'busulphan'[TIAB] OR 'carboplatin'[TIAB] OR 'cyclophosphamide'[TIAB] OR 'cytarabine'[TIAB] OR 'irinotecan'[TIAB] OR '6-mercaptopurine'[TIAB] OR 'clofarabine'[TIAB] OR 'topotecan'[TIAB] OR 'busulfan'[TIAB] OR 'vincristine'[TIAB] OR 'ifosfamide'[TIAB] OR 'doxorubicin'[TIAB]) AND ('0001/01/01'[PDAT]:'2012/10/01'[PDAT])

The search resulted in 117 hits on October 1 2012. After exclusion of review articles ($n$ = 3), animal studies ($n$ = 1), bio-analytical studies ($n$ = 1), articles in a language other than English ($n$ = 5), non-paediatric studies ($n$ = 6), non-drug studies ($n$ = 8), non-model based analyses ($n$ = 4), non-oncology studies ($n$ = 14) and other irrelevant articles ($n$ = 2), 73 hits remained, which were included in this review.

Publications were subsequently categorized based on drug, study characteristics (number of patients, study type, indication and study objectives) and analysis characteristics (analysis type, software, estimation method, model evaluation method, model type, covariates identified). For purposes of clarity, indications were only referenced if more than 10 patients of a particular indication were included.

## Results and discussion

An overview of the identified studies utilizing M&S-based approaches in paediatric oncology is depicted in Table 1. In Figure 3, the frequency of different drugs studied is

## Table 1

Overview of identified M&S-based publications in pediatric oncology

| Drug | Study characteristics | | | | | Analysis characteristics | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Nr. Pat (P/A)*† | *Age (years)*‡ | *Type*§ | *Indication*¶ | *Objectives*†† | *Type*‡‡ | *Software*§§ | *Evaluation*¶¶ | *Model*††† | *Covariates*‡‡‡ | |
| 6-MP | 19/0 | 10 (3–17) | Study | ALL | PK-Cov | PPK | NM (FOCE) | VPC, SPLIT | 1cmt M:1cmt | BSA, PGTPMT | Hawwa *et al.* [58] |
| Actinomycin D | 36/0 | 1.6–20.3 | Study | Oth | PK-Cov Contaminations | PPK | NM (FOCE) | VPC | 3cmt | BWT, AGE | Edwards [82] |
| Asparaginase | 168/0 | 5.8 (4–10.2) | Retro | ALL | PK-Cov | PPK | NM (FO) | | 1cmt | BSA | Hempel *et al.* [83] |
| Asparaginase | NA/0 | NA | NA | ALL | PdrK-Cov, SimDose | PPK | NM (SIM) | | 1cmt | | Avramis *et al.* [84] |
| Asparaginase | 118/0 | 5 (1–9) | Study | ALL | PK-Cov | PPK | NM (NS) | | 1cmtNL | | Avramis *et al.* [85] |
| Asparaginase | 32/0 | 4.5 (1–14) | Study | ALL | PK-Cov | PPK | NM (FOCE) | VPC, PPC | 2cmt | BSA, BWT | Borghorst *et al.* [86] |
| Busulfan | 24/0 | 6.3 (0.3–16.7) | Study | HSCT | PK-Cov, SimDose | PPK | NM (FOCE) | BS | 1cmt | BWT | Booth *et al.* [36] |
| Busulfan | 24/0 | 6 (0.5–16.7) | Retro | HSCT | PK-Cov, SimDose | PPK | NM (FOCE) | BS | 1cmt | BWT | Nguyen *et al.* [87] |
| Busulfan | 48/0 | 10.4 (0.4–18.1) | Retro | HSCT | PK-Cov | PPK | NM (FOCE) | | 1cmt | BSA | Schiltmeyer *et al.* [88] |
| Busulfan | 12/62 | 5.8 (1.3–12) | Retro | HSCT | PK-Cov, TDM | PPK | NM (FOCE) | | 1cmt | BWT, ALT, CMED | Sandstrom *et al.* [88] |
| Busulfan | 20/0 | 1.1 (0.1–7.8) | Study | HSCT | PK-Cov, LSS | PPK | NM (NS) | | 1cmt | BWT, DIS | Hassan *et al.* [89] |
| Busulfan | 94/0 | 9.2 (0.4–18.8) | Meta | HSCT | PK-Cov, SimDose | PPK | NM (FOCE) | VPC, SPLIT | 1cmt | BSA, BWT | Trame *et al.* [33] |
| Busulfan | 77/0 | 5 (0.2–23) | Meta | HSCT | PK-Cov | PPK | NM (FOCE) | VPC | 1cmt | BWT, PGGST | Zwaveling *et al.* [90] |
| Busulfan | 29/0 | 5.6 (0.1–18.3) | Study | HSCT | PK-Cov, SimDose | PPK | NM (FOCE) | VPC | 1cmt | Age, PGGST | Johnson *et al.* [64] |
| Busulfan | 103/0 | 1.5 (0.2–11.3) | Study | HSCT | PK-Cov | PPK | NM (FOCE) | BS | 1cmt | BWT, Age, CMED, FRM, DIS | Nakamura *et al.* [91] |
| Busulfan | 100/0 | 0.1 (5.3–18.1) | Study | HSCT | PK-Cov | PPK | USCP (NPAG) | | 1cmt | BWT, DIS | Bertholle *et al.* [92] |
| Busulfan | 6/0 | 6 (1.5–14) | Study | HSCT | PK-Cov, LSS | PPK | NM (FOCE) | | 1cmt | | Cremers *et al.* [60] |
| Busulfan | 48/0 | 2.5 (0.2–15) | Meta | HSCT | PK-Cov, SimDose | PPK | NM (NS) | VPC, SPLIT | 1cmt | BWT | Paci *et al.* [93] |
| Busulfan | 245/0* | (0.2–26) | Meta | HSCT | PK-Cov | PPK | NM (FOCE) | BS | 2cmt | BWT | Bartelink [94] |
| Busulfan | 158/0* | (0.1–26) | Meta | HSCT | PK-Cov | PPK | NM (FOCE) | External evaluation | 2cmt | BWT | Bartelink [95] |
| Busulfan | 63/0 | 3.0 (0.7–13) | Study | HSCT | PK-Cov | PPK | NM (FOCE) | | 1cmt | BWT | Veal [96] |
| Carboplatin | 13/56 | 31 (2–60) | Meta | NBL, Oth | PK-Cov, SimDose | PPK | NM (FOCE) | | 2cmt | HT, BWT, Age, CLCR, DUR | Lindauer *et al.* [97] |
| Carboplatin | 75/75 | 6.5 (1.2–17.5) | Retro | MED, NBL, Oth | PK-Cov | PPK | MPK (NS) | | 2cmt | BWT, SCR, NEPH | Urien *et al.* [98] |
| Carboplatin | 57/57 | 5 (0.2–18) | Retro | CNS, NBL, Oth | PK-Cov | PPK | NM (NS) | PPC | 2cmt | BWT, SCR, NEPH | Chatelut *et al.* [99] |
| Cisplatin | NA/0 | NA | NA | | PK-Cov | PBPK | NS (NA) | NA | PBPK | | Evans *et al.* [25] |
| Clofarabine | 40/0 | 12.3 (2–19) | Meta | ALL, AML | PK-Cov | PPK | NM (FOCE) | BS | 2cmt | BWT, WBC | Bonate *et al.* [55] |
| Cyclofosfamide | 15/0 | 13.3 (5.4–21) | Study | STS | PK-Cov | PPK | NM (FOCE) | | 1cmt | BSA, Sex | Chinnaswamy *et al.* [100] |
| Cyclofosfamide | 22/0 | 3.2 (1.3–9.4) | Study | NBL | PK-Cov | PPK | NM (FO) | VPC | 1cmtNL M:1cmt | GFR | McCune *et al.* [61] |
| Cytarabine | 52/0 | (0.2–19) | Meta | ALL, AML, Oth | PK-Cov | PPK | NM (FO) | | 2cmt M:1cmt | BSA, Age | Periclou *et al.* [101] |
| Daunorubicin | 24/0 | 15.4 (2.8–23.2) | Retro | AML, Oth | PK-Cov | PPK | NM (FOCE) | | 1cmt | BWT | Hempel *et al.* [102] |
| Daunorubicin | 33/0 | (0.1–18.8) | Meta | AML | PK-Cov | PPK | NM (FO) | | 2cmt M:1cmt | | Hempel *et al.* [103] |
| Doxorubicin | 22/0 | 15 (3.3–21.5) | Study | Oth | PK-Cov | PPK | NM (NS) | | 3cmt M:1cmt | BSA | Thompson *et al.* [62] |
| Erlotinib | 46/42 | (2–19) | Meta | CNS | PK-Cov, SkinTox | PPK | NM (FOCE) | VPC | 1cmt | BWT, PGCYP, PGABC | White *et al.* [74] |
| Etoposide | NA/0 | NA | NA | | PK-Cov | PBPK | PKSIM (NA) | NA | PBPK | | Kersting *et al.* [24] |
| Etoposide | 67/0 | 3.5 (0.3–16.7) | Study | MED, NBL, Oth | PK-Cov | PPK | MLX (SAEM) | VPC | 2cmt | BWT | Urien *et al.* [104] |
| Etoposide | 31/0 | 8 (0.8–23.7) | Retro | NBL, Oth | PK-Cov | PPK | Ppharm (NS) | VPC | 3cmt | BWT | Wurthwein *et al.* [105] |
| Etoposide | NA/0 | NA | NA | | PK-Cov, SimDose | SIM | Excel (NA) | NA | NA | | Wurthwein *et al.* [106] |
| Etoposide | 26/0 | 8.5 (2.0–19.0) | Study | SLT | PK-Cov | PPK | NM (FOCE) | VPC | 1cmt | | Baheti [107] |
| Ifosfamide | 32/0 | (1–18) | Study | Oth | PK-Cov | PPK | NM (FO) | | 1cmt M:1cmt | | Kerbusch *et al.* [108] |
| Imatinib | 41/0 | (6–24) | Meta | PHL, SLT | PK-Cov | PPK | NM (FOCE) | PPC | 1cmt M:2cmt | BWT | Menon *et al.* [109] |
| Irinotecan | 11/0 | 12 (3–17) | Study | SLT | PK-Cov | PPK | NM (FOCE) | | 2cmt | BWT | Kimura *et al.* [63] |
| Irinotecan | 82/0 | (1–21) | Study | SLT, Oth | PK-Cov | PPK | NM (FOCE) | PPC | 2cmt M:2cmt | BWT | Thompson *et al.* [110] |

## Table 1

Continued

| Drug | Study characteristics Nr. Pat (P/A)† | Age (years)‡ | Type§ | Indication¶ | Objectives†† | Analysis characteristics Type‡‡ | Software§§ | Evaluation¶¶ | Model††† | Covariates‡‡‡ | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Isotretinoin | 29/0 | 3.2 (1.1–18.7) | Study | NBL | PK-Cov | PPK | NM (FOCE) | | 1cmt | | Veal *et al*. [111] |
| Melphalan | 59/0 | 0 (0.3–18) | Study | HSCT | PK-Cov, LSS | PPK | NM (FOCE) | SPLIT | 2cmt | BWT, GFR, CMED | Nath *et al*. [112] |
| Methotrexate | 64/0 | 5 (1.6–16.8) | Retro | ALL, Oth | PK-Cov | PPK | NM (FOCE) | VPC | 2cmt | BWT, PGCT | Faganel *et al*. [113] |
| Methotrexate | 340/0 | 5 (0.4–17.8) | Study | ALL | PK-Cov, Relapse | PPK | NM (NS) | | 2cmt | BWT | Johnsson *et al*. [79] |
| Methotrexate | 69/0 | 6.7 (1–15) | Meta | ALL | PK-Cov, EFS | PPK | NM (NS) | | 2cmt | | Martelli *et al*. [80] |
| Methotrexate | 131/0 | (1.3–17.1) | Meta | ALL | PK-Cov, GITox | PPK | NM (FOCE) | | 2cmt | BWT, Age, DIS | Buitenkamp *et al*. [75] |
| Methotrexate | 118/0 | 7.4 (1.3–13.6) | Study | ALL | PK-Cov | PPK | NM (FOCE) | SPLIT | 2cmt | BSA, Age | Zhang *et al*. [114] |
| Methotrexate | 24/0 | 14.8 (10.8–18.8) | Retro | OSC | PK-Cov | PPK | NM (FOCE) | VPC, SPLIT | 2cmt | BWT, Age | Colom *et al*. [115] |
| Methotrexate | 79/0 | 6.9 (2–16) | Study | ALL | PK-Cov, LSS | PPK | NM (FOCE) | SPLIT | 2cmt | BWT | Plard *et al*. [116] |
| Methotrexate | 49/0 | 7 (0.5–17) | Retro | ALL | PK-Cov | PPK | NM (FOCE) | SPLIT | 2cmt | BWT, Age | Aumente *et al*. [117] |
| Methotrexate | NA/0 | NA | NA | | PK-Cov | PBPK | BM (NA) | NA | PBPK | | Li *et al*. [68] |
| Methotrexate | 23/0 | 6 (0.8–15) | Retro | ALL | PK-Cov, LSS | PPK | Ppharm (EM) | SPLIT | 2cmt | BWT, Age | Odoul *et al*. [118] |
| Methotrexate | 194/0 | NS (NS-NS) | Study | ALL | PK-Cov | PPK | ADAPT (MCPEM) | | 2cmt M:2cmt | DIS | Panetta *et al*. [67] |
| Methotrexate | 37/0 | 14 (4–21) | Retro | OSC, Oth | PK-Cov, MCT, RT, VOM | PPK | USCP (IT2B/NPEM) | | 2cmt | | Aquerreta *et al*. [76] |
| MK-0752 | 23/0 | 8.1 (2.6–17.1) | Study | CNS | PK-Cov | PPK | NM (FOCE) | | 1cmt | | Fouladi *et al*. [119] |
| Benzylguanine | 25/0 | NS (NS-21) | Study | CNS | PK-Cov, TDM | IPK | MLAB (NS) | | 1cmt M:1cmt | | Neville *et al*. [120] |
| Paclitaxel | 30/0 | (2.3–22.8) | Study | SLT | PK-Cov, NEUTR | IPK | ADAPT (ITS) | SPLIT | 2cmtNL | | Sonnichsen *et al*. [70] |
| Phenylacetate | 27/0 | 10 (1.4–20) | Study | Oth | PK-Cov, TDM | IPK | MLAB (NS) | | 1cmtNL M:1cmt | | Thompson *et al*. [121] |
| Prednisolone | 23/0 | 5.4 (2.4–15.2) | Study | ALL | PK-Cov, TDM | PPK | WNM (FO) | | 2cmt | BSA | Petersen *et al*. [122] |
| Pyrazoloacridine | 22/0 | (1–25) | Study | Oth | PK-Cov, NEUTR, TDM | IPK | MLAB (NS) | | 2cmt | | Berg *et al*. [69] |
| Temozolomide | 39/0 | 7.1 (0.7–21.9) | Study | CNS | PK-Cov | PPK | ADAPT (NS) | | 1cmt M:1cmt | BSA, Age | Panetta *et al*. [123] |
| Temozolomide | NA/0 | NA | NA | | PK-Cov, LSS | OD | ADAPT (Unknown) | | NA | | Kirstein *et al*. [124] |
| Thioguanine | 18/0 | 18 (4–25) | Study | Oth | PK-Cov | IPK | MLAB (NS) | | 2cmtNL | | Kitchen *et al*. [125] |
| Topotecan | 162/0 | 9.1 (0.1–22) | Meta | MED, NBL, SLT, Oth | PK-Cov | PPK | NM (NS) | BS | 2cmt | BSA, Age, GFR, CMED | Schaiquevich *et al*. [126] |
| Topotecan | 6/0 | 4.9 (3.2–8.4) | Study | MED | PK-Cov | PPK | ADAPT (MAP) | | 2cmt | | Freeman *et al*. [127] |
| Topotecan | 40/0 | 12 (3–20) | Retro | SLT | PK-Cov, NEUTR | IPK | ADAPT (NS) | | 2cmt | | Zamboni *et al*. [71] |
| Topotecan | 17/0 | 12 (1–16) | Meta | CNS | PK-Cov | IPK | ADAPT (MAP) | | 3cmt | | Baker *et al*. [128] |
| Vincristine | 26/0 | (2–16) | Study | SLT | PK-Cov | PPK | NM (NS) | VPC, BS | 2cmt | PGCYP, PGABC | Guilhaumou *et al*. [129] |
| Vincristine | 70/0 | (1–16) | Study | ALL | PK-Cov | IPK | ADAPT (MAP) | | 2cmt | | Groninger *et al*. [130] |
| Vincristine | 17/0 | 3.8 (1.3–12.4) | Study | ALL | PK-Cov | IPK | ADAPT (NS) | | 2cmt | | de Graaf *et al*. [131] |
| | NA/0 | NA | NA | | PK-Cov, TDM | PPK | NM (PRIOR) | | 1cmt | | Barrett *et al*. [81] |

Not specified (NS), Not applicable (NA). *Adult patients present but number of patients was not separately stated.. †Children *vs*. Adults. ‡Age, median (range), years, for paediatric subjects. If only other measure then median or range were available, these were used. §Study types were retrospective (Retro), pooled meta-analysis of multiple studies or datasets (Meta) or data collected as part of clinical study (Study). ¶Indications: Acute lymphoblastic leukemia (ALL), Haematopoietic stem cell transplantation (HSCT), Neuroblastoma (NBL), Other (Oth), Medulloblastoma (MED), CNS malignancy (CNS), Acute myeloid leukemia (AML), Soft tissue sarcoma (STS), Philadelphia positive leukemia (PHL), Solid tumor (SLT), Osteosarcoma (OSC). ††Study objectives: Characterize PK and/or covariates (PK-Cov), Limited sampling schedule (LSS), Therapeutic drug monitoring (TDM), Event-free survival (EFS), Gastrointestinal toxicitiy (GI-Tox), Mucosits (MCT), Renal toxicity (RT), Vomiting (VOM), Neutropenia (NEUTR). ‡‡Analysis types: Population pharmacokinetic/pharmacodynamic analysis (PPK), Individual level pharmacokinetic/pharmacodynamic (IPK) analysis, Physiologically-based pharmacokinetic model (PBPK), Optimal design (OD), Simulation study (SIM). §§Software and estimation methods: NONMEM (NM), Monolix (MLX), Berkeley Madonna (BM), USC-Pack (USCP), WinNonMix (WNM), First order conditional estimation (FOCE), First order estimation (FO), Simulation (SIM), Nonparametric estimation adaptive grid (NPAG), Stochastic approximation expectation maximization (SAEM), Expectation maximization (EM), Monte Carlo Parameteric Expectation Maximization Algorithm (MCPEM), Iterative two-stage Bayesian (IT2B), Non-parametric Expectation Maximization (NPEM,) Iterative two stage (ITS), Maximum a posteriori Bayesian estimation (MAP). ¶¶Model evaluation methods: Visual predictive check (VPC), External data or data-splitting procedure to evaluate model predictions (SPLIT), Posterior predictive check (PPC), Bootstrap analysis (BS). †††Model type: For parent drug and metabolite (M). One (1), two (2) and three (3) compartmental (cmt) models, that may have a non-linear (NL) element. ‡‡‡Covariates identified in the analysis: Body surface area (BSA), Pharmacogenetic factors for SNP or enzyme activity xx (PGxx), Total body weight (BWT), Alanine transaminase (ALT), Concomitant or prior drug effect (CMED), Disease related factors (DIS), Height (HT), creatinine clerance (CLCR), Serum creatinine (SCR), Formulation (FRM).

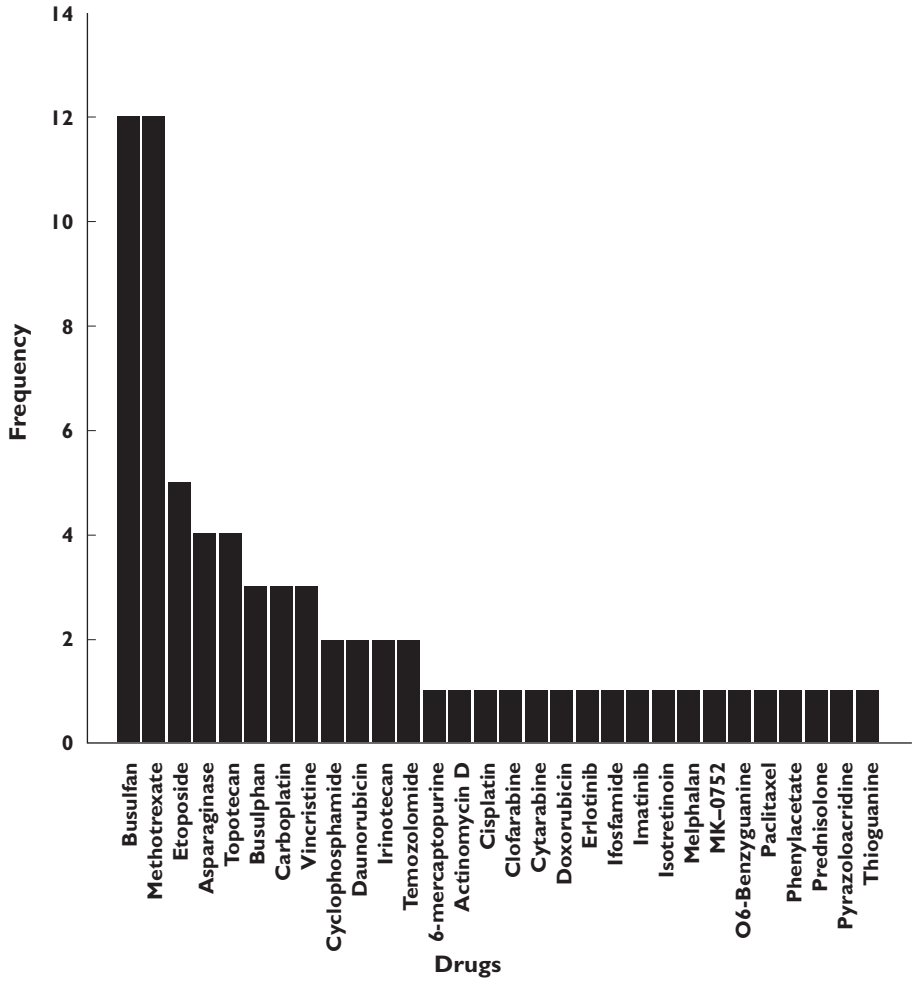


**Figure 3**

The frequency of anti-cancer drugs that were studied in the identified M&S-based analyses

depicted. Busulphan ($n$ = 15, 20%) and methotrexate ($n$ = 12, 16%) were the most frequently studied drugs. Also, multiple reports on etoposide ($n$ = 4, 5%), topotecan ($n$ = 4, 5%) and asparaginase ($n$ = 4, 5%) were described, while an additional number of drugs was studied less frequently. The most frequently investigated indication was acute lymphoblastic leukemia (ALL), which is also the most common malignancy diagnosed in children. A large number of studies reported small numbers of mixed indications, or various indications requiring haematopoietic stem cell transplantation (Figure 4). Most analyses were reported to be associated with a single study ($n$ = 37, 50%), while for 21% retrospective data collection was used. Combined (meta-) analysis of multiple studies was used for 13 studies. We also assessed the different model evaluation methods used (other than standard goodness of fit diagnostics), as depicted in Table 1.

The identified articles are discussed below in the context of the four earlier mentioned types of paediatric studies: (i) pharmacokinetic bridging studies, (ii) exposure–response studies, (iii) full drug development studies and (iv) drug treatment optimization studies. For each of these studies, we discuss the applications of M&S in paediatric oncology drug development, and also address potential opportunities for additional application of M&S techniques.

## *Pharmacokinetic bridging studies*

Three aspects of pharmacokinetic bridging studies are discussed: (i) determining starting dose in first-in-children PK studies, (ii) the procedure of dose regimen optimization during bridging and (iii) optimization of pharmacokinetic study designs.

*Scaling approaches to determine starting dose in first-in-children PK studies* Prior to commencement of a trial, appropriate starting dose levels in children have to be

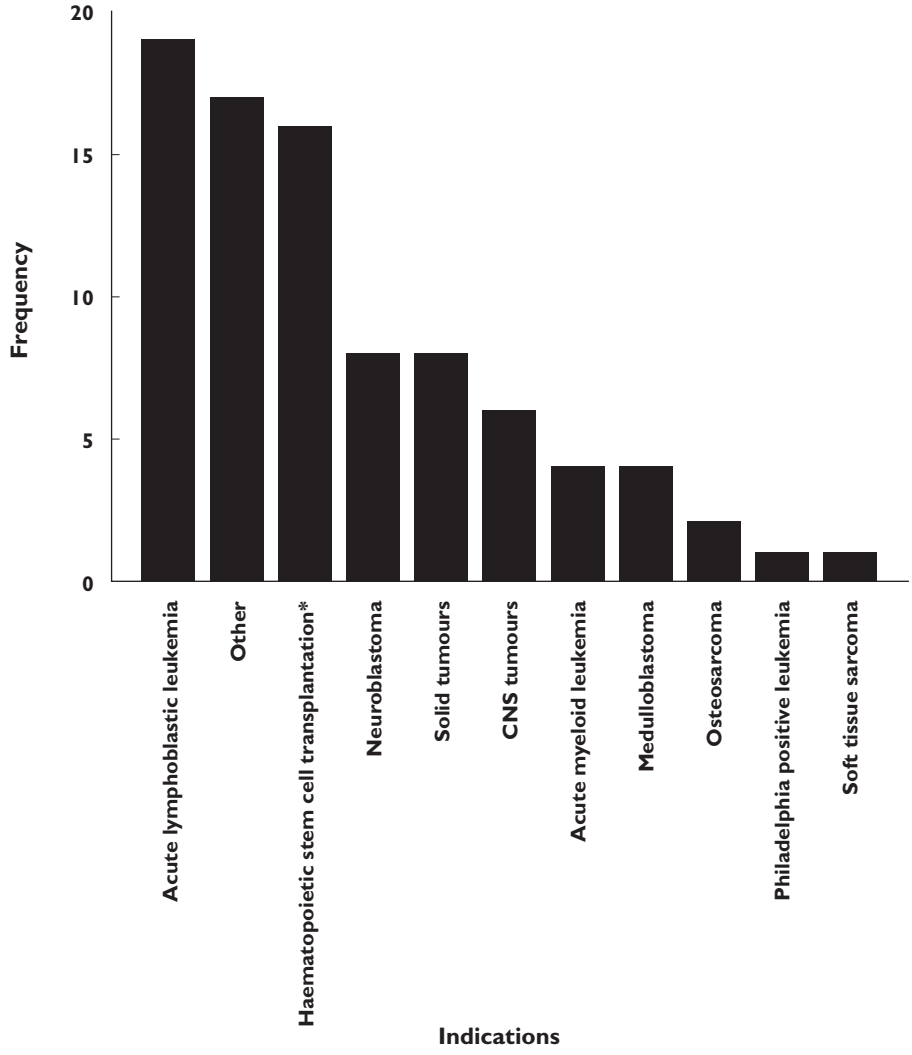


**Figure 4**

The frequency of different indications that were included in the identified M&S-based analyses. *Haematopoietic stem cell transplantation is no indication but a treatment for hematological malignancies

determined. Historically, paediatric starting dose levels have been frequently set at 80% of the maximum tolerated dose in adult patients [21], scaled by body surface area BSA. Nonetheless, considering the narrow therapeutic window of anti-cancer agents, the use of scaling approaches that are supported by a scientific rational and prior knowledge is of special importance in paediatric oncology. Here, we discuss the two most commonly used scaling approaches, namely PBPK and allometry, although alternative approaches in which literature data were leveraged in a more empirical fashion have also been described [22].

Physiologically-based PK models Physiologically-based PK (PBPK) models are multi-compartmental models that represent the major tissues, organs and drug effect pathways in an organism, that allow prediction of drug PK. These predictions are based on the physiological characteristics of tissues, and intrinsic physicochemical drug properties. A recent review has described the value of PBPK modelling in the paediatric population in more detail [23]. In paediatric oncology, only three examples of PBPK modelling were identified.

Kersting *et al*. [24] described a PK bridging study where etoposide PK in children was predicted incorporating literature information of relevant drug metabolizing enzymes and age-dependent protein binding. The model predictions were compared with observed data in both children and adults and indicated adequate predictions across age. This example demonstrates how prior knowledge about physiology can be used to yield reasonable predictions of PK, and such approaches can thus potentially be applied for other drugs as well.

Evans *et al*. described a relatively simple PBPK model which predicted the concentration–time profiles of both free and total cisplatin in young children and adolescents [25]. They showed how the model predictions adequately matched observed PK data in 14 patients. The described model structure was based on a model originally developed in dogs, and contained a limited number of compartments for plasma, skin, muscle, liver, gastrointestinal tract and kidneys. Subsequently, the model parameters were adjusted to reflect human paediatric physiology. Interesting in this approach was the adjustment of a model originally developed in animals, and how such an approach can also be used to make predictions on expected PK in the paediatric population.

Given the complexity of the different dynamical changes during paediatric development, PBPK methods are of special relevance in paediatric bridging studies for establishing a first-in-children dose. Rationally deriving a clinically relevant yet safe starting dose in paediatric oncology is complex, due to the small therapeutic windows of anti-cancer drugs, and frequently applied combination treatments. Here, PBPK methods can potentially be very useful because they allow incorporation of relevant physiological knowledge. Out of the scope of oncology, PBPK models have been successfully applied in the area of paediatric pharmacology for a number of examples [23, 26, 27]. Application in paediatric oncology has thus far been limited, yet examples described can be considered promising.

Allometric scaling Allometric scaling concerns the relationship between size and changes in physiology. It has been shown how size correlates with metabolic processes [28], based on a power relationship. The principles of allometry can be used for scaling clearance and volume between adults and children with respect to size and may therefore be a useful pharmacometric scaling tool in potentially determining rational starting doses when conducting a trial in children [29, 30]. Although there is still debate [31] on the value of the allometric exponent on clearance, typically an estimate of 0.75 is used.

In the identified analyses in this review, allometric relationships with body weight were included very frequently ($n$ = 33, 45%). In addition BSA was also frequently included as a covariate, and it has been shown that the relation between clearance and BSA is similar to allometric scaling using body weight (with an exponent of 0.75 on CL) [32]. An illustrative example was provided by Trame *et al*. [33], who investigated different strategies for dosing regimen individualization for busulfan in paediatric oncology patients. They found that both BSA and allometric scaling-based dose regimens were adequate and similar for individualizing busulfan pharmacotherapy in children.

A recent comparison between allometric scaling and physiologically-based PK modelling for determining the first dose in children found that allometric scaling may not always be optimal in obtaining appropriate dose levels for children, especially in very young children [34], because this method does not take into account specific physiological changes relevant to drug exposure. In addition, an empirical comparison between allometry and PBPK in drug development showed that in general the performance was comparable, but that the magnitude of error in predicted exposure was much higher when using allometry [35], therefore in some cases leading to ineffective or toxic dose levels. These differences can most likely be attributed to the lack of specifically acknowledging developmental changes in metabolic capacity or organ function in the case of allometric scaling. Nonetheless, allometric scaling approaches do offer relatively simple ways to predict PK parameters in children to determine the paediatric starting dose, and can be incorporated in adult population PK models in a straightforward fashion.

*Dose regimen optimization during bridging* Although a substantial number of identified M&S-based analyses aimed to characterize PK to optimize paediatric dosing regimens, however this was in most cases not in the context of an explicitly conducted paediatric bridging study. Rather, *post hoc* optimization of dose regimens of drugs already in use has been conducted.

One clear example where population PK M&S was used extensively in paediatric drug development was for i.v. busulfan. M&S-based analyses supported both paediatric labeing in the US [36] and Europe [37]. The publication from Nguyen *et al*. [37] clearly described the application of M&S during the paediatric development. Population PK–PD M&S allowed characterization of inter-individual variability and understanding of associated patient related determinants of this variability. Subsequently, with a simulation analysis, optimal dosing regimens were derived across different age groups. The report by Nguyen *et al*. is illustrative because it clearly demonstrates the impact of M&S in the context of the paediatric clinical drug development process where adult human exposure needed to be bridged to paediatric patients, and to derive optimal paediatric dose regimens.

The population PK–PD models extensively used in the analysis by Nguyen, but also in most other analyses identified, involved compartmental PK models that employed non-linear mixed effect (NLME) modelling, in which different levels of variability can be estimated, and which allow analysis of sparsely sampled datasets [38]. Because of these advantages, most of the identified M&S analyses ($n$ = 59, 80%) used a NLME approach to analyze the data and to characterize inter-individual variability. The majority of identified analyses used NONMEM ($n$ = 50, 68%) or ADAPT ($n$ = 9, 10%) for data analysis, while the remaining analyses ($n$ = 15, 21%) used a broad range of less frequently used software packages.

*Informative sampling designs* Recently, Foo *et al*. [39] suggested an adaptive optimal design methodology for paediatric PK bridging studies which allowed adjustment of optimal study designs during execution of the trial, adaptively assessing when sufficient paediatric patients were included in a clinical trial. Although this example was only described in the context of a simulation study, it is potentially promising because it aims to optimize the number of paediatric patients in a clinical study combined with the often limited number of patients available with paediatric malignancies.

The applied method in the aforementioned example, optimal design, is a statistical methodology that aims to optimize a study design with respect to a design criterion [40]. To define an optimal design, a prior model is necessary. Most commonly, optimal designs have been applied to optimize parameter estimation precision, in order to identify optimal sparse sampling designs that allow adequate estimation precision. Optimal design methods may, however, also be used to optimize other design parameters such as number of subjects, groups, dose levels or even study power [41]. Because of the practical and ethical limitations of PK studies in the paediatric oncology population, optimal design approaches can be especially relevant, in order to allow informative studies with minimal sampling and/or subjects.

A challenge to the application of optimal design (or any other design optimization method), is that prior knowledge (e.g. prior model) may sometimes be limited, which complicates application of such design optimization methods. If no prior model is available, it could potentially be considered to use a PBPK model to support the optimization [27]. In addition, especially in paediatric oncology, the number of practical restrictions in terms of study design can be substantial, thereby restricting the design space to optimize a clinical study design.

In our review, however, we did not identify any studies that applied optimal design to derive optimal sparse sampling schedules, or any other design optimization, although the benefit of such methods has been demonstrated in adults [39, 42–45]. Given the limited number of patients frequently available and potential other limitations in paediatric oncology drug development, design of an informative clinical study design is important and optimal design or approaches such as clinical trial simulation can be relevant tools to optimize clinical study designs where feasible.

## *Exposure–response studies*

Development of biomarkers for treatment response in paediatric oncology is an active field, with many recent and potentially promising developments [46–49]. In adult oncology, exposure–response models have been developed [50, 51]. However in this review focusing on paediatric oncology, exposure–response models for biomarkers (potentially) predictive for efficacy were not identified.

Nonetheless, development of biomarkers as surrogate measures of efficacy is of special importance for the evaluation of anti-cancer drugs in children. Although phase II studies frequently use outcome-based measures such as progression free survival (PFS), other, longitudinal continuous (bio-) markers could potentially be more informative and sensitive measures in early phase clinical trials. For instance Bruno *et al*. [52] suggested the use of change in tumour size as a more informative endpoint of phase II trials. Additionally, when analyzing biomarkers in a model-based framework, measures of outcome (e.g. PFS, overall survival (OS)) may be linked to biomarkers of disease progression. In adult oncology for instance, Claret *et al*. [53] developed PK–PD-outcome models that quantify the relationship between drug exposure, tumour growth inhibition and outcome (PFS/OS). Thus, recent developments in adult oncology indicate potentially promising results of exposure–response modelling of anti-cancer drugs, but unfortunately no applications have been reported yet in the development of paediatric anti-cancer drugs.

## *Full drug development studies*

One example of a paediatric anti-cancer drug in which M&S has supported a full drug development study, was the development of clofarabine [54, 55], which was first approved by the FDA for acute lymphoblastic leukemia (ALL) in paediatric patients instead of an adult indication [56]. Bonate *et al*. described a population PK analysis of clofarabine and intracellular clofarabine triphosphates, based on available data from multiple clinical studies in paediatric patients, also identifying predictors of inter-individual variability [55]. In this study, it was shown that both the white blood cell count and body weight were clinically important predictors for the expected drug exposure. This analysis was later also extended with adult data and the metabolite 6-ketoclofarabine [54].

Paediatric drug development studies generally suffer from increased risks for dropout, but also large (age-related) variability in patient characteristics, which may in turn affect the outcome of a clinical trial. In addition, for full drug development studies in which PK, safety and efficacy are characterized, substantial numbers of patients and time are required. Therefore, specifically, the conduct of such studies in the area of paediatric oncology is highly challenging, and unexpected events or other sources of variability may impact on the outcome of a clinical trial. Specifically for such trials, clinical trial simulation (CTS) is a M&S methodology which may be considered for *a priori* evaluation of the likelihood of a trial meeting its objectives, because it allows evaluation of the impact of variability introduced by a range of unexpected events during trial execution (subject dropout, missed samples, lack of compliance) [57]. In CTS, a clinical trial with the expected exposure and/or response profiles of individual patients can be simulated, using developed exposure–response models. Subsequently, random events such as missing data can be

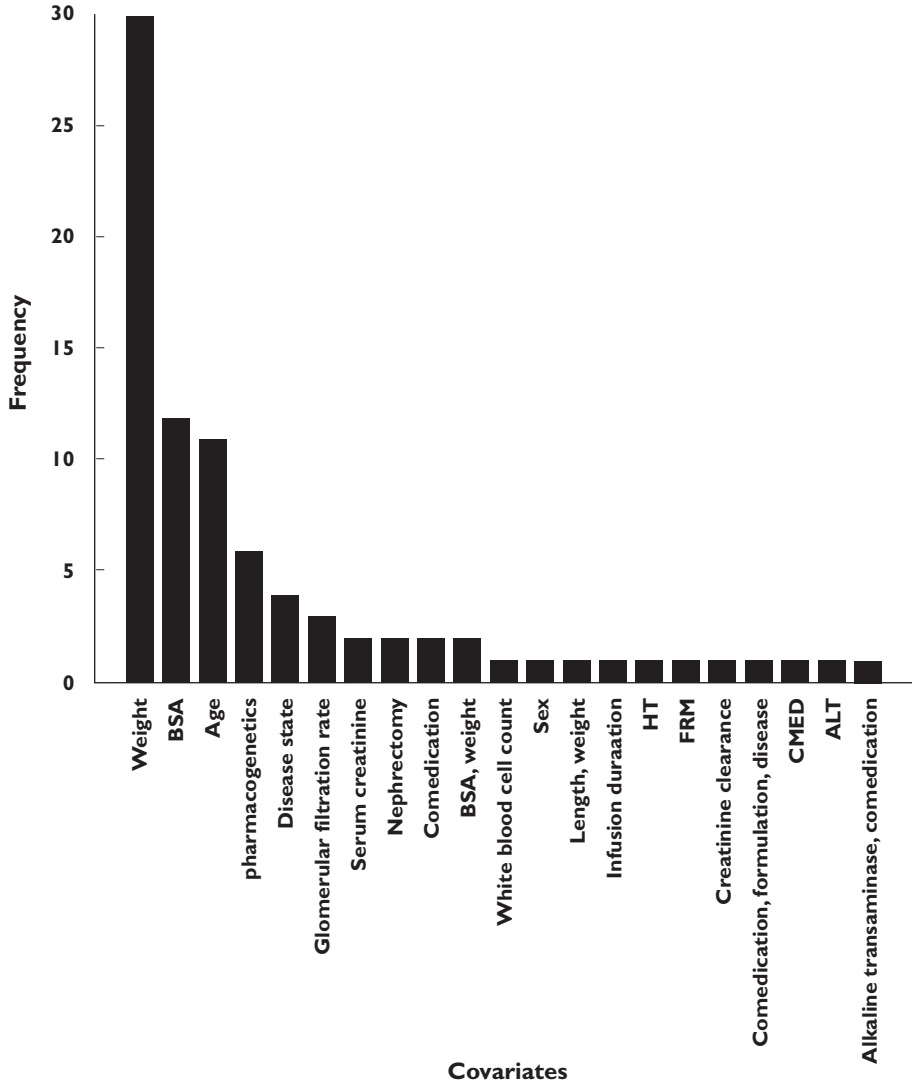


**Figure 5**

The frequency covariates that were included in the identified M&S-based analyses. ALT, alanine transaminase; BSA, body surface area; CMED, comedication; FRM, formulation; HT, height

applied to the dataset, and subsequently the obtained simulated trial data can be analyzed using the planned statistical analysis procedures. In the context of paediatric oncology however, CTS approaches have not been reported.

## *Drug treatment optimization studies*

Even if a drug is already clinically used, paediatric dosing regimens of anti-cancer agents can potentially be optimized further with respect to either pharmacokinetics (e.g. target exposures), or with respect to toxicity profiles or based on ultimate outcome (e.g. efficacy measures). In such treatment optimization studies, it is often important to understand and quantify variability between patients, which is why population PK–PD methods are frequently applied.

*Optimization of pharmacokinetics* Most of the studies ($n$ = 59 80%) which were identified in this review (Table 1) descriptively analyzed PK in paediatric oncology patients using population PK modelling approaches, with the ultimate aim to identify patient covariates predictive for inter-individual variability in PK parameters. The analyses identified were generally built using either therapeutic drug monitoring (TDM) data or data obtained from phase I studies.

The frequency of inclusion of various patient characteristics as covariates is illustrated in Figure 5. In seven studies (9.5%), adult data were also co-analyzed, which could be considered a useful approach to support characterization of body size and maturation effects on PK parameters. In some studies [58–64], covariates predictive of inter-individual variability in PK parameters were investigated

while the sample size was relatively small. However, accurate identification of covariate effects requires a representative distribution of the covariate of interest. Thus, conclusions related to influential covariates derived from such studies should be considered carefully [65].

Eleven studies developed population PK models to develop or optimize TDM or limited sampling (LS) strategies. In this context, M&S can be used, for instance, to perform simulations studies to evaluate the success rate of different TDM or LS strategies. Additionally, optimal design techniques may be used to derive the most informative sampling times for obtaining information about the expected drug exposure. Specifically for TDM approaches, inter-occasion variability (IOV) is an important component of variability to consider, because it may inflate residual variability estimates and cause bias in parameter estimates [66]. When IOV is large, TDM strategies may be less useful. Yet, a substantial number of the identified analyses did not report evaluation of IOV (70%), although in some cases this may be related to availability of only single occasion data.

Recently, integration of physiological components for dose optimization strategies in the context of paediatric oncology was demonstrated by Panetta *et al*. who described an analysis in which the intracellular PK of methotrexate metabolites in leukemia cells was characterized, and related to ALL cell lineages. Also a folate-pathway model was included in this framework to derive optimal treatment schedules [67]. Overall this analysis demonstrated how insight can be obtained into intracellular pharmacology of drugs and the relationship with treatment efficacy.

PBPK methods can also be used to investigate the impact on PK for specific conditions. Li *et al*. used PBPK modeling to investigate specifically the effect of malignant effusions in paediatric oncology patients on the disposition of methotrexate [68]. Thus even when a general paediatric dose regimen has already been established, additional co-morbidities may arise that will further affect PK and of which the effect may not be comparable between adults and children. Since PBPK methods aim to represent human physiology, these models can be adapted to include representations of any relevant factors such as the investigated effect of malignant effusion in this example.

*Optimization for toxicity and outcome measures* A limited number of studies was performed specifically describing models for toxicity or outcome measures ($n$ = 7). Haematological toxicity is a commonly occurring dose-limiting toxicity for many anti-cancer drugs. Exposure–response models describing the time course and variability of blood cell counts may therefore be useful to optimize treatment with respect to the incidence of severe haematological toxicity. In the field of paediatric oncology, Berg *et al*. [69] first described the relationship between decrease in absolute neutrophil count and exposure to pyrazolacridine in children and young adults using an empirical *post hoc* sigmoid $E_{max}$ model, which allowed assessment of limiting exposure levels in these patients. Later, Sonnichsen *et al*. [70] described the actual time course of the neutrophil count. However in this analysis, the authors did not consider the impact of exposure on the shape (e.g. magnitude of decrease) of the neutrophil count time course, which limits the use of such a model in investigating alternative dose regimens. Finally Zamboni *et al*. [71] also described the time course of neutropenia induced by topotecan using a model with a number of transit compartments. This analysis also incorporated the relationship between drug exposure and the response in neutrophil count decline, allowing the model to be used for investigation of alternative dose regimens. In adult oncology, Friberg *et al*. [72] developed a model similar to the analysis described by Zamboni *et al*. also incorporating transit compartments accounting for the maturation process of neutrophils in the bone marrow. The model by Friberg *et al*. was, however, developed in the context of population PK–PD modelling, allowing improved quantification of variability and analysis of more sparse data, which is frequently the case for clinical data of haematological toxicity. The model by Friberg *et al*. (Figure 6) is now considered to be well established as it has been applied to a range of anti-cancer agents. Very recently, an adapted version of the model by Friberg *et al*. has also been implemented for paediatric oncology patients [73] for topotecan. Potentially, (paediatric) maturational effects of haematopoesis could also be incorporated in this model, but it has not yet been investigated if such effects are present and clinically relevant.

Model-based analyses have also been reported for other types of toxicities in paediatric oncology. Usually, these were implemented as *post hoc* logistic regression analyses linking exposure to the probability of toxicity, in contrast to the more integrated models as described for haematological toxicity. For instance White-Koning *et al*. reported on a exposure–response model for erlotinib-induced skin toxicity in adult and paediatric patients [74]. In this PK–PD analysis, it was demonstrated that the higher recommended dose in children compared with adults for erlotinib is mainly due to pharmacokinetic rather than pharmacodynamic differences. Another PK–PD model in paediatric cancer patients was reported that described the relationship between methotrexate exposure and the probability of gastrointestinal toxicity in patients with and without Down's syndrome [75]. Patients with Down's syndrome have decreased tolerance to methotrexate, but this analysis allowed exclusion of the impact of pharmacokinetic differences between patients with and without this syndrome. Finally, Aquerreta *et al*. [76] developed a combined PK–PD model quantifying the probability for developing renal toxicity, mucositis and vomiting for paediatric oncology patients treated with methotrexate. The model could be used to optimize rationally high dose

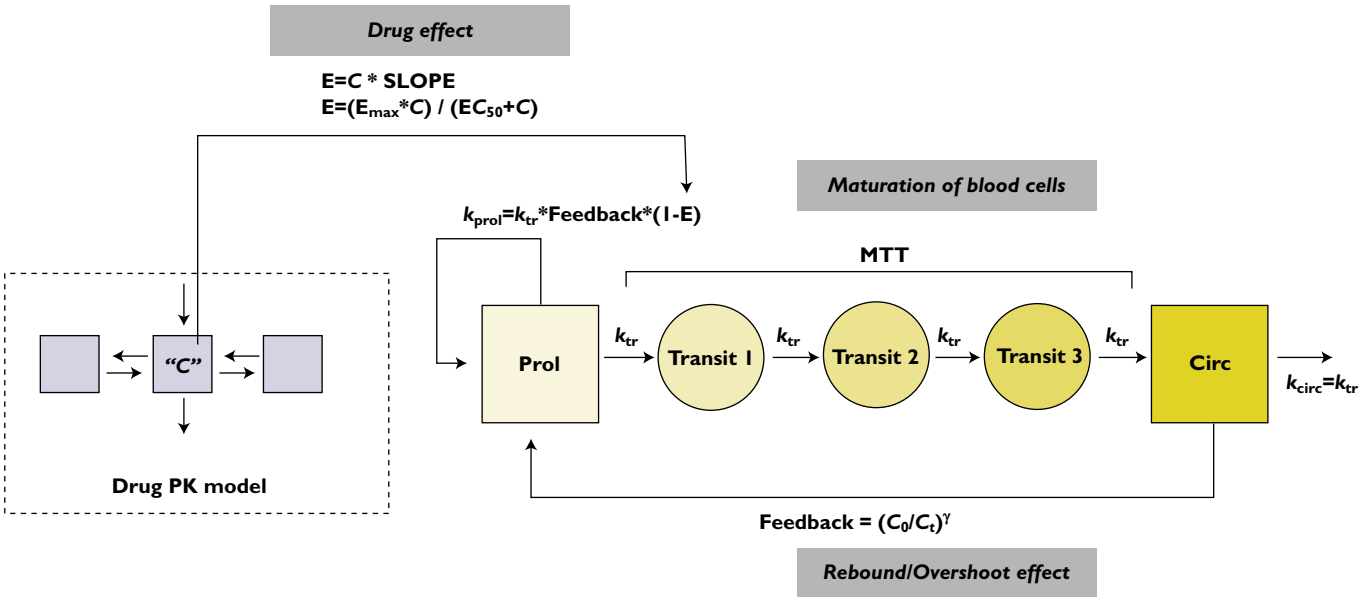


**Figure 6**

Semi-physiological model for haematological toxicity developed by Friberg *et al*. for adult patients. $C$ = Drug concentration, E = Effect, $E_{max}$ = Maximum effect, $EC_{50}$ = Half-maximum effect concentration, SLOPE = Drug effect, $k_{tr}$ = Transition rate constant, MTT = Mean transition time

methotrexate treatment, and it also confirmed upper thresholds of methotrexate plasma concentrations that should be avoided in paediatric patients.

With the increasing survival of paediatric oncology patients, the long term cardiac toxicity of anthracyclines is receiving substantial interest. Recently in adults an exposure–response study for cardiotoxicity was described and utilized to optimize treatment [77, 78]. A similar approach could also be of relevance in the paediatric oncology population.

In summary, a number of illustrative examples have been published demonstrating how PK–PD models for toxicity can be developed for paediatric oncology patients, to help in the understanding of potential mechanisms or factors that may play a role in the development of various toxicities. Nonetheless, the applications are limited compared with the much larger number of exposure–toxicity analyses that have been described for adults. The ultimate application of such models by optimizing dosing regimens for toxicity have however not been conducted. One possible exception is the study by Panetta *et al*. [73], who described a population PK–PD model that incorporated a tumour growth inhibition model based on paediatric xenograft data, together with a (clinical) model for topotecan-induced neutropenia, in order to investigate optimal treatment regimens taking into account both efficacy and toxicity in paediatric patients with neuroblastoma. This analysis demonstrated how useful computational approaches can be in evaluating potential dose regimens and for leveraging of preclinical data. Nonetheless, this example has not yet been verified or supported by a clinical study or any other clinical observations.

Besides toxicity, *post hoc* logistic regression analyses have also been reported for measures of outcome. Jönson *et al*. [79] reported a model-based analysis accounting for the probability of relapse after methotrexate. It was found that dosing regimens based on body weight for methotrexate may give more predictable PK but could potentially also improve outcome measures in these patients. Furthermore, Martelli *et al*. considered inclusion of event-free survival in their PK analysis [80], but here no clear relationship could be identified.

Finally, an example of the link of model-based analysis and routine patient care was recently provided by Barrett *et al*. [81], who described the integration of hospital database systems with a Bayesian model-based framework for determination of optimal dose adjustment strategies in individual patients. They showed how the management of paediatric drug treatment can be greatly enhanced by the use of this system, especially for drugs with narrow therapeutic windows that may easily lead to suboptimal treatment or toxicities.

## Conclusion

We reviewed the application of M&S-based analysis in paediatric oncology in the context of the four types of clinical studies that can typically be performed: PK bridging studies, exposure–response analyses, full drug

development studies and drug treatment optimization studies. M&S-based approaches have been used successfully in other areas of paediatric drug development and in adult-oncology, but the application of M&S to support paediatric drug development proactively has been very limited.

Overall, most studies identified were descriptive PK studies that aimed to characterize PK in paediatric patients, and to identify potential predictors of variability in PK parameters, in order to optimize further dose regimens of already clinically used drugs or to optimize TDM strategies of such drugs. Although these analyses have been useful to further optimize drug treatment, formal analyses related to bridging of exposure were much more limited. The clinical development of busulphan and clofarabine are illustrative examples for the overall role M&S approaches can play in a clinical drug development process.

The use of PBPK modelling for first-in-children dose selection is promising, but only a limited number of examples have currently been published, most likely because this is a relatively new development in the field of quantitative clinical pharmacology. Although in many cases, conventional empirical dose selection approaches [21] may still be considered, scaling methods such as PBPK could be useful to provide scientific support for the selected starting dose-level.

With respect to exposure–response studies, no reports in paediatric oncology have been described. Nonetheless, exposure–response analyses could still be considered promising when biomarkers in paediatric patients are further developed, but this task is complex also due to the intrinsic differences in disease biology between children and adults.

Given the low incidence of paediatric malignancies and ethical and practical constraints in this particularly sensitive group of patients, efficient design and analysis of clinical studies is crucial, and M&S approaches can potentially support and streamline the paediatric drug development process of anti-cancer drugs, since they allow integration of (prior) knowledge, efficient analysis of sparse or heterogeneous data, and can be used to support decision making, thereby stressing the relevance of these methods to be used more in the field of paediatric oncology drug development

## Competing Interests

All authors have completed the Unified Competing Interest form at httpwww.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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