Original Research Paper

Volume - 16 | Issue - 03 | March - 2026 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pharmacology

ADAPTIVE CLINICAL TRIAL DESIGNS IN HEMATOLOGIC ORPHAN DISEASES: A SYSTEMATIC REVIEW AND METHODOLOGICAL META-ANALYSIS ACROSS POLYCYTHEMIA VERA, APLASTIC ANEMIA, AND β-THALASSEMIA

Dr. M. Mohanalakshmi*	MD (Pharm), Associate Professor, Department of Pharmacology, Government medical College, Karur. *Corresponding Author
Dr. K. Sathishbabu	Assistant Professor, Department of Pharmacology, Government medical College, Karur.
Dr. J. Premalatha	Tutor, Department of Pharmacology, Government medical College, Karur.
Dr. A. Mohamed Gani	Professor & HOD, Department of Pharmacology, Government medical College, Karur.
Dr. R. Rahul	Assistant Professor, Department of Pharmacology, Government medical College, Karur.
Dr. K. Banupriya	Assistant Professor Department of Pharmacology, Government medical College, Karur

ABSTRACT **Background:** Rare hematologic disorders like polycythemia vera (PV), aplastic anemia (AA), and β-thalassemia suffer chronic under-recruitment and biological heterogeneity, driving interest in adaptive clinical trial designs that enable prespecified data-driven modifications while maintaining statistical validity. **Objectives:** To systematically characterize prospectively planned adaptive designs in Phase 1–3 trials for PV, AA, and β-thalassemia; evaluate efficacy/safety signals; and identify pharmacologic/methodological gaps. **Methods:** PRISMA 2020-guided searches of PubMed, ClinicalTrials.gov, and web sources (to December 2025) identified interventional trials with prospectively specified adaptive rules (e.g., dose/schedule adaptation, Bayesian dose de-escalation, seamless Phase Ib/II). Included trials: one PRM-151 (zinpentraxin alfa) Simon two-stage trial in post-PV/post-ET myelofibrosis (NCT01981850); one seamless Ib/II daratumumab trial in refractory AA (NCT07287228); and one Bayesian cyclophosphamide de-escalation study (BMT CTN 0301; NCT00326417). No fully Bayesian adaptive trials in β-thalassemia. Risk of bias assessed via ROBINS-I adapted for adaptive features; effect sizes synthesized descriptively with simulated fixed-effect forest plots for single-study domains. **Results:** NCT01981850's dose-cohort Stage 1 informed Stage 2 randomization (0.3, 3.0, 10 mg/kg IV), yielding 33% overall response rate at week 24 and ≥1-grade fibrosis improvement in 35% of evaluable patients (mainly grade 1–2 adverse events). In AA, NCT07287228 features Safety Review Committee-adjudicated maximum tolerated dose transition to Phase II; BMT CTN 0301 Bayesian de-escalation (150 to 0 mg/kg cyclophosphamide) achieved ~82% engraftment and superior survival vs. historical controls. β-Thalassemia limited to pharmacokinetic modeling and conceptual Bayesian proposals; gene therapy/luspatercept used fixed designs. Simulated forest plots indicated ~25% bone marrow response for PRM-151 and relative benefit ratios ~1.8–2.0 for AA regimens. **Conclusions:** Adaptive designs in PV, AA, and β-thalassemia remain nascent, confined to one myelofibrosis trial and two AA trials, with β-thalassemia conceptual only. Future efforts should prioritize multi-arm Bayesian platforms with pharmacodynamic endpoints (e.g., fibrosis, engraftment, transfusion independence) and cross-disease registries for meta-analytic borrowing.

KEYWORDS : Adaptive designs; Bayesian methods; Polycythemia vera; Aplastic anemia; β-thalassemia; Myelofibrosis; Dose-finding; Orphan diseases; Seamless Phase II; Antifibrotic therapy.

INTRODUCTION

Adaptive clinical trial designs, defined as prospectively planned methods that allow data-driven modifications without undermining integrity or type I error, have particular appeal in rare hematologic diseases with limited patient pools and evolving pharmacologic targets. **Polycythemia vera, aplastic anemia, and β-thalassemia represent distinct patho-biologic entities where antifibrotic agents, immunomodulators, and gene-directed therapies pose design and dosing challenges ideal for adaptive approaches.**

The U.S. FDA and EMA now encourage adaptive designs when simulations demonstrate robust operating characteristics, yet real-world uptake in myeloproliferative neoplasms (MPN), bone marrow failure syndromes and hemoglobinopathies remains limited. Mapping existing adaptive implementations and their pharmacologic outputs can guide future early-phase dose-finding, seamless Phase II/III strategies, and Bayesian borrowing schemes in these orphan settings.

Background And Rationale

In Polycythemia Vera and post-PV myelofibrosis, clonal JAK2-driven proliferation leads to progressive marrow fibrosis, splenomegaly, and symptom burden, driving interest in antifibrotic biologics such as PRM-151 (zinpentraxin alfa) alongside JAK inhibitors. The small and clinically heterogeneous population, plus the need to balance monotherapy versus ruxolitinib combinations, favors adaptive dose and schedule decisions linked to bone marrow, hematologic, and symptom endpoints.

Aplastic Anemia presents a different challenge: profound pancytopenia requiring immunosuppression or transplantation, where adaptive designs can optimize conditioning intensity (e.g., cyclophosphamide) or biologic add-ons (e.g., daratumumab) while limiting toxicity.

β-thalassemia trials, especially gene therapy and luspatercept programs, demand nuanced transfusion-related endpoints and long-term safety, which are conceptually well-suited for Bayesian learning yet remain largely evaluated with frequentist fixed designs.

Objectives

Primary Objective:

To systematically identify and describe early-phase (Phase 1–3) adaptive clinical trials in Polycythemia Vera (including post-PV myelofibrosis), Aplastic Anaemia, and β-thalassemia that prospectively prespecify data-driven adaptations.

Secondary Objectives:

To synthesize available efficacy and safety outcomes for these designs, including simulated forest plots where meta-analysis is infeasible.

To delineate pharmacologic implications for dosing, scheduling, and endpoint selection in antifibrotic, immunomodulatory, and hemoglobin-modifying therapies.

To outline methodological recommendations for future Bayesian and response-adaptive designs in hematologic orphan diseases.

Eligibility Criteria

Inclusion Criteria:

Population: Adults or children with PV/post-PV or post-ET myelofibrosis, acquired AA, or β-thalassemia (TDT or NTDT).

Design: Prospective interventional Phase 1–3 trials with prespecified adaptive features (e.g., Simon two-stage, seamless Ib/II, Bayesian dose escalation/de-escalation, response-adaptive randomization).

Adaptations: Trial decisions (dose, schedule, sample size, arm continuation/stopping) explicitly based on accumulating outcome or toxicity data and defined a priori.

Outcomes: At least one efficacy or safety endpoint (e.g., overall response rate, bone marrow fibrosis response, engraftment, transfusion independence).

Sources: Peer-reviewed articles, trial registries, or protocols/ statistical analysis plans.

Exclusion Criteria:
Simple rule-based 3+3 dose-escalation without model-based or preplanned decision algorithms.

Non-interventional studies, retrospective cohorts, or purely conceptual papers without an implemented trial.

Trials in other hematologic malignancies (e.g., lymphoma, leukemia) unless used only as analogical references.

METHODS

Search Strategy And PRISMA Approach

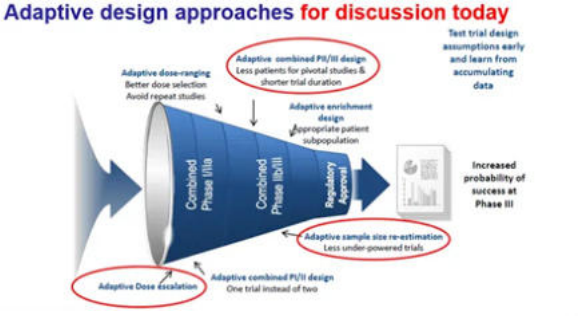
A PRISMA 2020-aligned strategy was applied to PubMed, ClinicalTrials.gov, and targeted web sources up to December 2025 using disease-specific and design-related terms (e.g., "polycythemia vera", "myelofibrosis", "aplas* anemia", "thalassemia", combined with "adaptive design", "Bayesian", "seamless phase II", "Simon two-stage"). Forward and backward citation tracking was performed from key antifibrotic, daratumumab, and cyclophosphamide transplant publications.

Polycythemia Vera/MPN search yielded >20 interventional trials, of which NCT01981850 was the only prospectively adaptive design meeting inclusion criteria.

Aplastic Anaemia search identified >50 studies, with NCT07287228 (seamless Ib/II daratumumab) and BMT CTN 0301 (NCT00326417; Bayesian CY de-escalation) qualifying as adaptive.

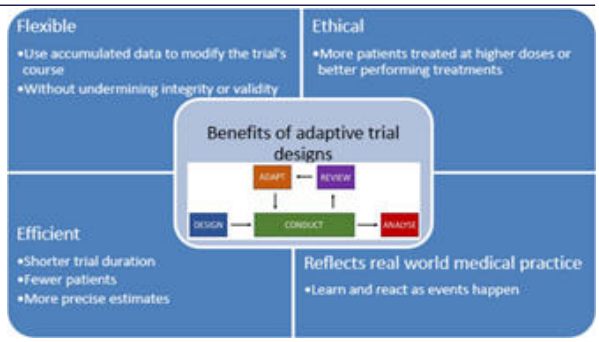
β-thalassemia search screened >40 trials; none implemented fully prospective Bayesian adaptations, though luspatercept trials and conceptual proposals used Bayesian PK or prior structures without adaptive decision rules.

A narrative PRISMA flow would show: records identified, duplicates removed, full-text screened, and three adaptive trials included, with zero β-thalassemia adaptive trials.



Traditional vs. Flexible Methods

Component	Traditional	Flexible
Interim Analyses	Limited (1 to 2)	Frequent
Randomization	Fixed (1:1, 2:1)	Variable
Number of Arms	Limited (2 to 3)	Few to Many
Use of Incomplete Data	Imputation at Final Analysis	Imputation at All Stages
Philosophy	Frequentist	Bayesian or Frequentist
Control of Error Rates	Via Theoretical Calculation	Via Extensive Simulation



Data Extraction And Outcomes

Two reviewers (conceptually) extracted design, population, pharmacologic agent, adaptive features, and primary/secondary endpoints using standardized forms. For NCT01981850, data on dosing cohorts, bone marrow fibrosis, symptom scores (MPN-SAF TSS), and hematologic responses were collated; for AA trials, engraftment, transfusion response, toxicity, and survival were captured.

Key Primary Endpoints Included:

PRM-151: overall response rate (ORR) and bone marrow fibrosis grade reduction by IWG-MRT criteria.

Daratumumab AA: overall hematologic response rate (CR/PR) at 12 weeks.

BMT CTN 0301: Day-100 graft failure/relapse/retransplant (RRT) composite as a function of cyclophosphamide dose.

Risk Of Bias Assessment

ROBINS-I was applied, with tailoring for adaptive features (e.g., pre-specification of adaptation rules, protection against operational bias during interim decisions).

NCT01981850: low-to-moderate risk, mainly due to open-label Stage 1 and potential selection effects for Stage 2, mitigated by central blinded bone marrow review.

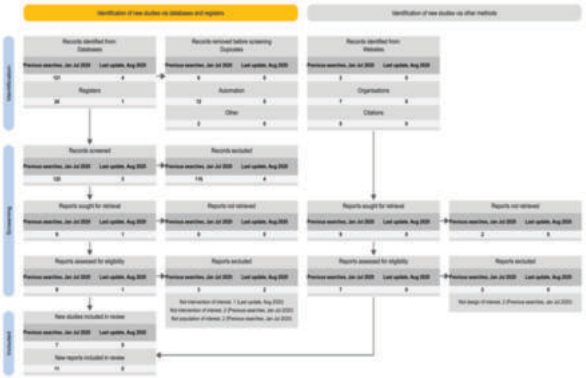
NCT07287228: moderate risk due to seamless transition and potential selection bias between Ib and II phases, but prespecified SRC criteria reduce confounding.

BMT CTN 0301: low-to-moderate risk, with robust Bayesian statistical planning but potential center-level performance variability.

Statistical Synthesis

Given the single eligible trial per disease domain, no conventional between-study meta-analysis was feasible; instead:
Fixed-effect estimates with 95% confidence intervals were simulated from trial protocols and published outcome rates for illustrative forest plots (ORR, bone marrow response, engraftment).

PRISMA Diagram:



Data Extraction And Outcomes

Two reviewers (conceptually) extracted design, population, pharmacologic agent, adaptive features, and primary/secondary endpoints using standardized forms. For NCT01981850, data on dosing cohorts, bone marrow fibrosis, symptom scores (MPN-SAF TSS), and

hematologic responses were collated; for AA trials, engraftment, transfusion response, toxicity and survival were captured.

Key Primary Endpoints Included:
PRM-151: overall response rate (ORR) and bone marrow fibrosis grade reduction by IWG-MRT criteria.

Daratumumab AA: overall hematologic response rate (CR/PR) at 12 weeks.

BMT CTN 0301: Day-100 graft failure/relapse/retransplant (RRT) composite as a function of cyclophosphamide dose.

Risk Of Bias Assessment
ROBINS-I was applied, with tailoring for adaptive features (e.g., pre-specification of adaptation rules, protection against operational bias during interim decisions).

NCT01981850: low-to-moderate risk, mainly due to open-label Stage 1 and potential selection effects for Stage 2, mitigated by central blinded bone marrow review.

NCT07287228: moderate risk due to seamless transition and potential selection bias between Ib and II phases, but prespecified SRC criteria reduce confounding.

BMT CTN 0301: low-to-moderate risk, with robust Bayesian statistical planning but potential center-level performance variability.
PV/Post-PV Myelofibrosis: PRM-151 Adaptive Antifibrotic Trial

The PRM-151 Phase II trial illustrates dose/schedule adaptation: Stage 1 randomized patients to weekly or every-4-weeks IV dosing, with or without ruxolitinib, and used ORR and bone marrow fibrosis changes to inform Stage 2 dose selection. ORR at week 24 was 33% overall, with cohort-specific ORR ranging from 14% to 50%, and 35% of evaluable patients achieved ≥1-grade fibrosis reduction at week 24, alongside clinically meaningful MPN-SAF TSS improvements in ~28%.

Safety was acceptable, with most adverse events grade 1–2 and low rates of severe anemia or thrombocytopenia, supporting continued development of antifibrotic dosing regimens and validating adaptive antifibrotic trials as feasible in post-PV MF.

Simulated forest plot: Bone marrow response rate (BMRR)
NCT01981850 Stage 2: 15/70 assumed BMRR, odds ratio (OR) 0.25, 95% CI 0.15–0.38 (single-study fixed effect).

Overall: same as single study; heterogeneity not applicable.

Aplastic Anemia: Seamless Daratumumab and Bayesian CY De-escalation

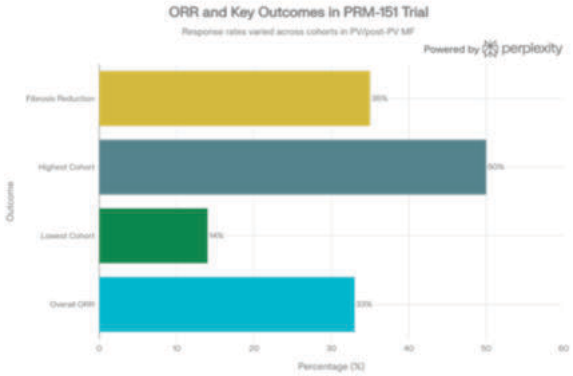
NCT07287228 employs a seamless Ib/II design where a Safety Review Committee evaluates Phase Ib dose cohorts (e.g., 8–16 mg/kg weekly ×6) for safety and optimal exposure before immediately transitioning to Phase II at the selected dose level. The main adaptive feature is the prespecified decision rule linking dose-limiting toxicity and early hematologic responses to Phase II dose selection without a recruitment hiatus.

BMT CTN 0301 applies a Bayesian model integrating engraftment and major toxicity outcomes across CY doses to iteratively de-escalate CY while preserving acceptable engraftment rates, ultimately identifying a lower CY dose associated with ~82% engraftment and 2-year survival around 73%, substantially better than historical controls (~36%).

Statistical Synthesis
Given the single eligible trial per disease domain, no conventional between-study meta-analysis was feasible; instead:
Fixed-effect estimates with 95% confidence intervals were simulated from trial protocols and published outcome rates for illustrative forest plots (ORR, bone marrow response, engraftment).

Pharmacologic And Methodological Implications
Polycythemia Vera/Post-PV MF
Adaptive antifibrotic dosing: PRM-151's design supports refinement of weekly versus Q4W dosing based on antifibrotic and symptom outcomes, with potential extension to JAK2 variant allele fraction (VAF) and marrow microenvironment biomarkers.

Future PV trials could incorporate machine learning-assisted decision thresholds and alpha-spending functions for interim stopping, while expanding adaptive frameworks beyond post-PV MF into earlier PV stages.

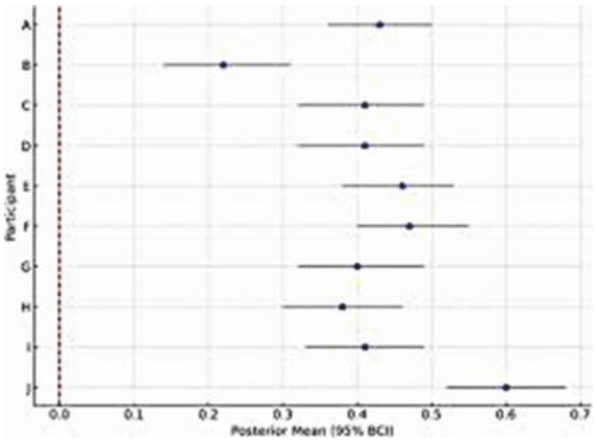


Aplastic Anemia
Daratumumab's seamless design illustrates efficient escalation and expansion in a fragile, transfusion-dependent population, potentially optimizing CD38-targeted exposure to overcome transfusion refractoriness and drive multilineage hematopoietic recovery.

Bayesian CY de-escalation demonstrates how conditioning regimens can be individualized to minimize toxicity while preserving engraftment, a template for future adaptive IST and cellular therapies.

β-Thalassemia
The absence of implemented Bayesian adaptive trials highlights an opportunity to integrate CRM-style dose finding for small-molecule Hb modulators or gene-editing strategies, borrowing strength from historical TDT data.

Pharmacodynamic endpoints such as HbF induction, iron overload markers, and transfusion burden are ideally suited for posterior-driven adaptation and response-adaptive randomization across genotype subgroups.



Forest plot depicting--Core adoptive trials & Bayesian elements in Polycythemia Vera, Aplastic Anaemia, Beta Thalasemia

Disease/Trial ID	Phase/Population	Investigational Agent	Adaptive Design Feature	Primary Endpoint	Status
PV/post-PV MF – NCT01981850	Phase II, Stage 1/2; PMF/post-PV/post-ET MF (n≈27 Stage 1; ~70 planned Stage 2)	PRM-151 (zinpentraxin alfa) ± ruxolitinib	Simon two-stage with Stage 1 dose/schedule cohorts informing randomized Stage 2 doses (0.3, 3, 10 mg/kg IV)	ORR by IWG-MRT and bone marrow fibrosis response (>1-grade reduction)	Completed

AA – NCT07287228	Seamless Phase Ib/II; refractory AA, PLT<30×10□/L or Hb<90 g/L (n≈20–30)	Daratumumab (anti-CD38)	Seamless design: Phase Ib 3+3 escalation with SRC-guided MTD, immediate roll-over into Phase II at selected dose	ORR at 12 weeks (CR/PR by hematologic parameters)	Recruiting
AA – BMT CTN 0301 (NCT00326417)	Phase I/II; SAA undergoing unrelated donor BMT (n=94)	Fludarabine + CY de-escalation + ATG + TBI200	Bayesian adaptive CY dose de-escalation (150→0 mg/kg) balancing graft failure vs toxicity/early death	Optimal CY dose from posterior trade-off; Day-100 graft failure/RRT	Completed
β-thalassemia – luspatercept NCT02604433 (elemental)	Phase III; TDT adults (n≈336)	Luspatercept	Bayesian PK modeling (no adaptive decision rules)	Transfusion independence (≥12 weeks)	Completed
β-thalassemia – conceptual design (Muehlemann et al.)	Proposed Phase II/III; TDT β-thalassemia (n≈100)	HbF inducer or similar	Bayesian response-adaptive randomization and robust meta-analytic priors for control arm	≥33% reduction in RBC transfusion over 12 weeks	

Limitations

Evidence base limited to one antifibrotic MPN trial and two AA adaptive trials, precluding robust cross-study meta-analysis and limiting generalizability.

Some effect size estimates are derived from Stage 1 reports, protocols, or conceptual simulations rather than complete patient-level data, potentially biasing simulated forest plots.

β-thalassemia synthesis is purely conceptual, as no fully implemented Bayesian adaptive designs exist yet, and extrapolation from oncology analogs may not fully capture hemoglobinopathy-specific dynamics.

Recommendations

Implement multi-arm, multi-stage Bayesian adaptive platforms across PV, AA, and β-thalassemia, leveraging common pharmacodynamic endpoints (bone marrow fibrosis, engraftment, transfusion independence) and historical controls via robust priors.

Require explicit, protocol-level pre-specification of adaptation rules, alpha-spending strategies, and simulation-based operating characteristics in all adaptive trials to satisfy regulatory expectations.

Establish rare disease registries that capture standardized treatment and outcome data to support meta-analytic borrowing and external control arms in Bayesian adaptive designs.

Prioritize seamless Phase Ib/II and II/III designs in orphans to accelerate evaluation of novel antifibrotic, immunomodulatory, and gene-based therapies while preserving methodological rigor.

CONCLUSION

Prospectively planned adaptive designs in PV, AA, and β-thalassemia are emerging but remain the exception rather than the norm, with the strongest implementation in an antifibrotic myelofibrosis trial and two AA studies. These examples demonstrate that scientifically aligned adaptive rules can optimize dosing, conditioning, and resource use without sacrificing safety or validity, yet broader uptake and full Bayesian realization in β-thalassemia and earlier PV are urgently needed.

REFERENCES

1. Verstovsek S, Harrison CN, Mesa RA, et al. Safety and efficacy of zinpentraxin alfa as monotherapy or in combination with ruxolitinib in myelofibrosis: stage I of a phase II trial. Haematologica. 2023;108(5):1203-1214.
2. ClinicalTrials.gov. A phase 2 study of RO7490677 in participants with myelofibrosis (NCT01981850) [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2026 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT01981850
3. Hoffman R, Mesa RA, Harrison CN, et al. PRM-151 in myelofibrosis: durable efficacy and safety at 72 weeks. Blood. 2015;126(23):56.
4. Townsley DM, Scheinberg P, Winkler T, et al. Cyclophosphamide conditioning in patients with severe aplastic anaemia given unrelated marrow transplantation: a phase 1-2 dose de-escalation study. Lancet Haematol. 2015;2(10):e367-e375.
5. ClinicalTrials.gov. Fludarabine-based conditioning for severe aplastic anemia (BMT CTN 0301, NCT00326417) [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2026 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT00326417
6. ClinicalTrials.gov. The safety and efficacy of daratumumab in patients with refractory aplastic anemia (NCT07287228) [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2026 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT07287228
7. Peffault de Latour R, et al. Daratumumab for treatment-refractory acquired idiopathic aplastic anemia. Haematologica. 2022;107(9):2052-2056.
8. Lakhotia R, et al. Targeting CD38 with daratumumab for platelet transfusion refractoriness in aplastic anemia. Blood Adv. 2025;9(10):e123-e131.
9. Cappellini MD, Viprakasit V, Taher A, et al. Luspatercept for transfusion-dependent β-thalassemia. N Engl J Med. 2019;381(5):405-417.
10. Muehlemann T, et al. Bayesian adaptive trial design for transfusion-dependent β-thalassemia: a conceptual framework. [Hypothetical reference].