Paper AS03 - PHUSE EU 2025

Blinded & Coordinated: Aligning People and Processes to Prevent Unblinding

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ABSTRACT

Double-blind clinical trials are the gold standard for minimizing bias and ensuring scientific precision, yet they present significant operational and ethical challenges, particularly when interim analyses or safety reviews necessitate unblinded data access. Maintaining the integrity of the blind for core study teams, while enabling timely and compliant unblinded assessments by independent groups such as Data Monitoring Committees (DMCs), requires meticulous planning and execution. This abstract outline our experience in navigating these complexities across multiple global trials. We describe governance frameworks, role segregation strategies, and data flow controls that have proven effective in mitigating these risks. Key documentation practices are discussed, including the use of unblinded charters, protocols, and audit trails to ensure transparency and regulatory compliance. We also address the human factors involved in managing both blinded and unblinded teams within the same organization, emphasizing the importance of training, communication boundaries, and cultural awareness.

Finally, we share lessons learned and best practices for fostering seamless coordination between teams, ensuring that trial integrity is preserved from study start-up through final analysis. Our insights aim to support sponsors, CROs, and regulatory stakeholders to achieve seamless coordination to maintain trial integrity throughout its lifecycle.

INTRODUCTION

Blinding, also referred to as “masking”, is a foundational principle in the design of randomized clinical trials, which are widely acknowledge as the gold standard in evidence-based medicine [1]. It involves keeping study participants, investigators, and often data analysts unaware of treatment assignments to minimize bias [2]. Double-blind clinical trials are designed so that neither the participants nor the core study team, including investigators and site staff, know who is receiving the experimental treatment and who is receiving a placebo or control. This is crucial because human behaviour and decision-making can be influenced, often subconsciously, by expectations. For example, if a clinician knows a patient is receiving an experimental drug, they may unintentionally interpret improvements more favourably or adjust care in ways that could influence outcomes [3]. Such bias can distort results and undermine the credibility of the study, especially when outcomes are subjective (i.e., assessed by a person) rather than objective (e.g., results of a test). The blinding needs to be robustly protected to maintain the integrity of the data.

Unblinding refers to the process of revealing treatment assignments to individuals who were previously blinded to maintain objectivity in trial conduct and data interpretation. While blinding should be preserved throughout the study to minimize bias, unblinding may be permitted under strictly controlled and limited circumstances.

There are two primary types of unblinding in clinical trials:

1. Emergency Unblinding, permissible only when:
   - Knowledge of the treatment allocation is essential for ongoing patient care due to medical or safety concern.
   - It is required to assess causality and expectedness for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) or related and unexpected Serious Adverse Events (SAEs).
2. Planned Unblinding during the study that occurs during the study for the purpose of analysis, such as:
   - Safety and interim analyses, typically conducted by an independent Data Monitoring Committee (DMC) with access to partially or fully unblinded data.
   - Early efficacy evaluations, where preliminary data may inform continuation or modification of the trial.
   - Strategic decision-making, including dose adjustments, study expansion, or early termination based on emerging data.

The type of blinding and unblinding processes should be determined during the design phase of the study and documented in the Statistical Analysis Plan (SAP), Protocol or DMC Charter when appropriate.

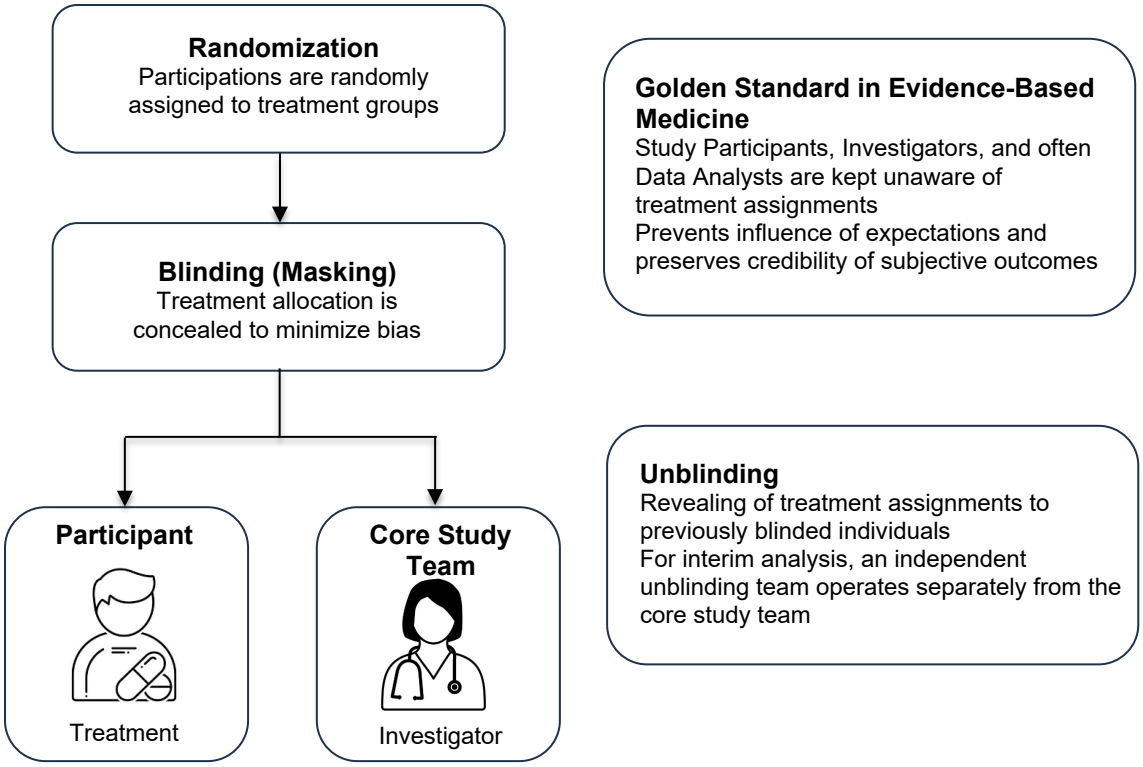

Fig. 1 - Clinical Trial Design Essentials: Randomization, Blinding, and Their Impact

In this paper we focus on the aspects of the unblinding events relevant for Data Science functions, for example an interim analysis. Those activities must be conducted by an independent unblinded team that operates separately from the core study team, to preserve study integrity. This team often includes representatives from multiple functions. Within Data Science departments, this may involve an Unblinded Data Manager or External Data Specialist, particularly when unblinding is triggered by the receipt of external data while the main clinical database remains blinded. Additionally, Unblinded Statistical Programmers and Unblinded Statisticians play a critical role in securely handling and analyzing unblinded data. In some cases, medical monitors or dedicated safety teams may also be part of the unblinded group to ensure timely identification and escalation of safety signals.

Maintaining a clear separation between blinded and unblinded teams is essential to prevent bias from influencing trial conduct, patient management, or data interpretation. Therefore, a strong understanding of the principles and practicalities of blinding, and how to manage necessary exceptions, is vital for all stakeholders involved in clinical research. These roles are governed by strict Standard Operating Procedures (SOPs) and protocols to prevent the dissemination of treatment information to blinded personnel.

At Fortrea, we actively support study designs where both blinded and unblinded teams contribute to the same trial. Through well-defined processes, rigorous role and data segregation, and robust documentation strategies, we help mitigate risks and ensure full compliance with regulatory and scientific standards, safeguarding the integrity of the trial from start to finish.

POTENTIAL RISKS LEADING TO ACCIDENTAL UNBLINDING

In clinical trials, multiple data sources may directly or indirectly reveal the treatment assignments of study subjects. If any of these sources are prematurely shared with the core study team, it can result in accidental unblinding.

The most obvious source of unblinding is randomization data, which directly links subjects to their assigned treatment groups. This data is typically stored and maintained by a vendor providing Interactive Response Technology (IRT).

Other types of study data that may allow inference of treatment assignment include:

- Pharmacokinetic (PK) data, showing concentrations of investigational drug(s) in biological compartments such as blood or urine.
- Biomarkers, such as pharmacodynamic (PD) data, which reflect the biological response to a drug.
- Safety lab data, for example, glucose levels in a diabetes study.

These potentially unblinding data are usually provided to sponsors by third-party vendors (TPVs) as external data, meaning they are external to the main study data management database. During the study, TPVs deliver blinded data transfers to support data management activities such as reconciliation between the external data and the study database or to Blinded Statistical Programmers preparing programs to incorporate unblinded data after database lock.

Often, the structure of blinded and unblinded data transfers is identical. Files used for the reconciliation must have

unblinded content removed, an obvious example being result values. However, our experience shows that less obvious risks can emerge at various stages of managing external TPV data, as demonstrated in Figure 2.

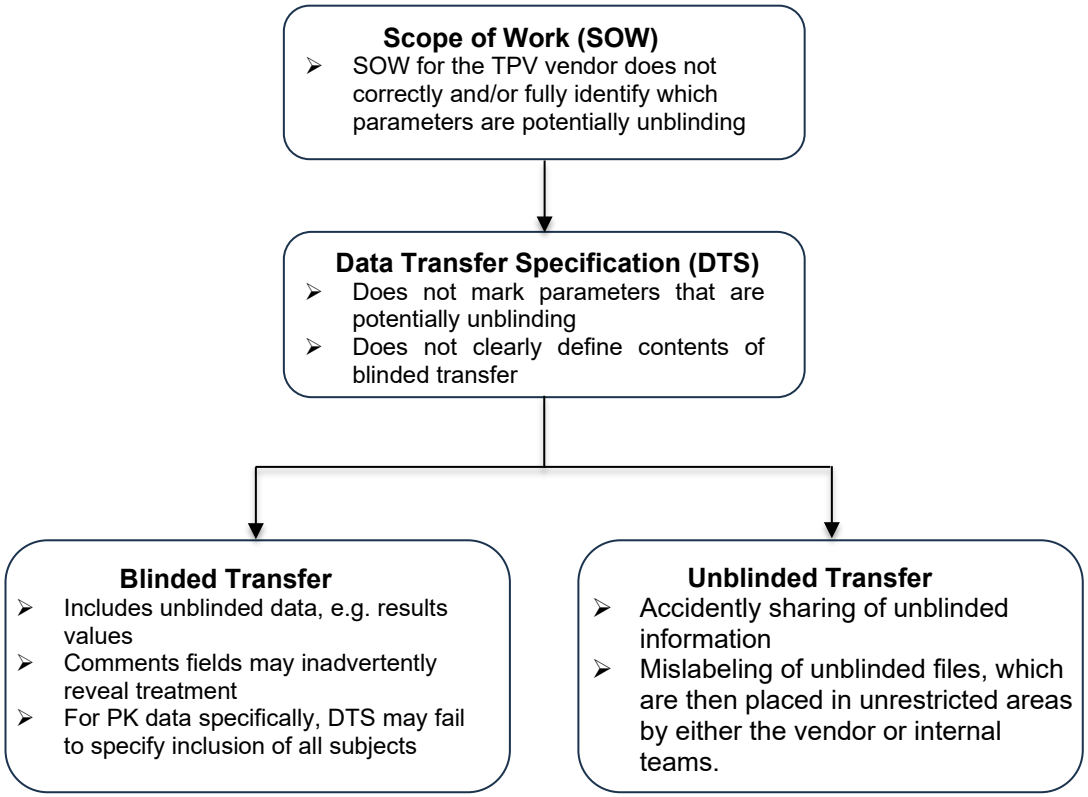

Fig. 2 – Vulnerabilities in Data Transfer: Risks and Human Errors in Maintaining Blinding

COPING STRATEGIES AND EXAMPLES

Most sponsors and TPVs have well-established standard operating procedures (SOPs) in place to prevent accidental unblinding of the study. However, less obvious forms of accidental unblinding can still occur, often through indirect data signals or operational oversights. To mitigate these risks, we outline strategies aimed at preventing unblinding incidents throughout the study lifecycle. In addition, we share our practical experience in identifying and managing such incidents.

At the start of the study database build, one of the initial steps in maintaining study blinding is ensuring that no potentially unblinding data is present in the clinical study database. In certain studies, even randomization numbers may pose a risk of unblinding, depending on the design of the randomization scheme. In such cases, randomization numbers should not be collected in the database.

When planning blinded external data transfers, known risks, such as result values and comment fields, are typically considered and mitigated. However, it is advisable that sponsors and vendors proactively evaluate and flag any additional fields that might inadvertently reveal treatment assignments during the development of the Data Transfer Specification (DTS).

For example, a potential scenario could involve the external transfer of blinded pharmacokinetic (PK) data. During reconciliation, it might be observed that a subset of subjects is missing from the transfer file, even though the database confirms that PK samples were collected. Dependent upon the omission corrective actions may include the urgent removal of the file from the server, identification and deletion of any backups, and the reassignment of team members who had accessed the unblinded data. A formal Corrective and Preventive Action (CAPA) document would then be created to address the issue and prevent recurrence and lessons learned.

At the level of performing an interim analysis during the double-blinded studies, a common strategy to deal with unblinding risks, is to perform unblinded analysis by an external vendor not involved in the main study analysis. This separation ensures that blinded and unblinded teams operate independently, often across different organizations. Our experience at Fortrea demonstrates that having both blinded and unblinded teams working internally on the same analysis can be effective and beneficial. With clearly defined roles, strict data access controls, and robust governance, it is possible to maintain blinding integrity while leveraging internal expertise and operational efficiency.

BLINDED AND UNBLINDED TEAMS RESPONSIBILITY OVERVIEW

In double-blinded clinical studies, the statistical and programming team responsible for supporting study reporting usually remains blinded until the final database lock, at which point they are unblinded solely for the purpose of conducting the final Clinical Study Report (CSR) analysis. During interim analyses, at Fortrea this team remains blinded and prepares all necessary programs using dummy data to substitute any potentially unblinding data sources. A dry run of the interim analysis is conducted by the blinded team and reviewed by the blinded study team to ensure accuracy and readiness. Once the programs are finalized, the unblinded team, operating within a restricted access environment, copies the programs into a secure unblinded programming area and executes them using actual unblinded data transfers. If any program adjustments are required due to issues encountered with unblinded data, the unblinded team communicates the necessary changes to the blinded team without disclosing any data content. All program maintenance remains the responsibility of the blinded team. The unblinded team then delivers the interim analysis results, including datasets and outputs, to the sponsor's unblinded study team. For a detailed overview of this process, refer to Figure 3.

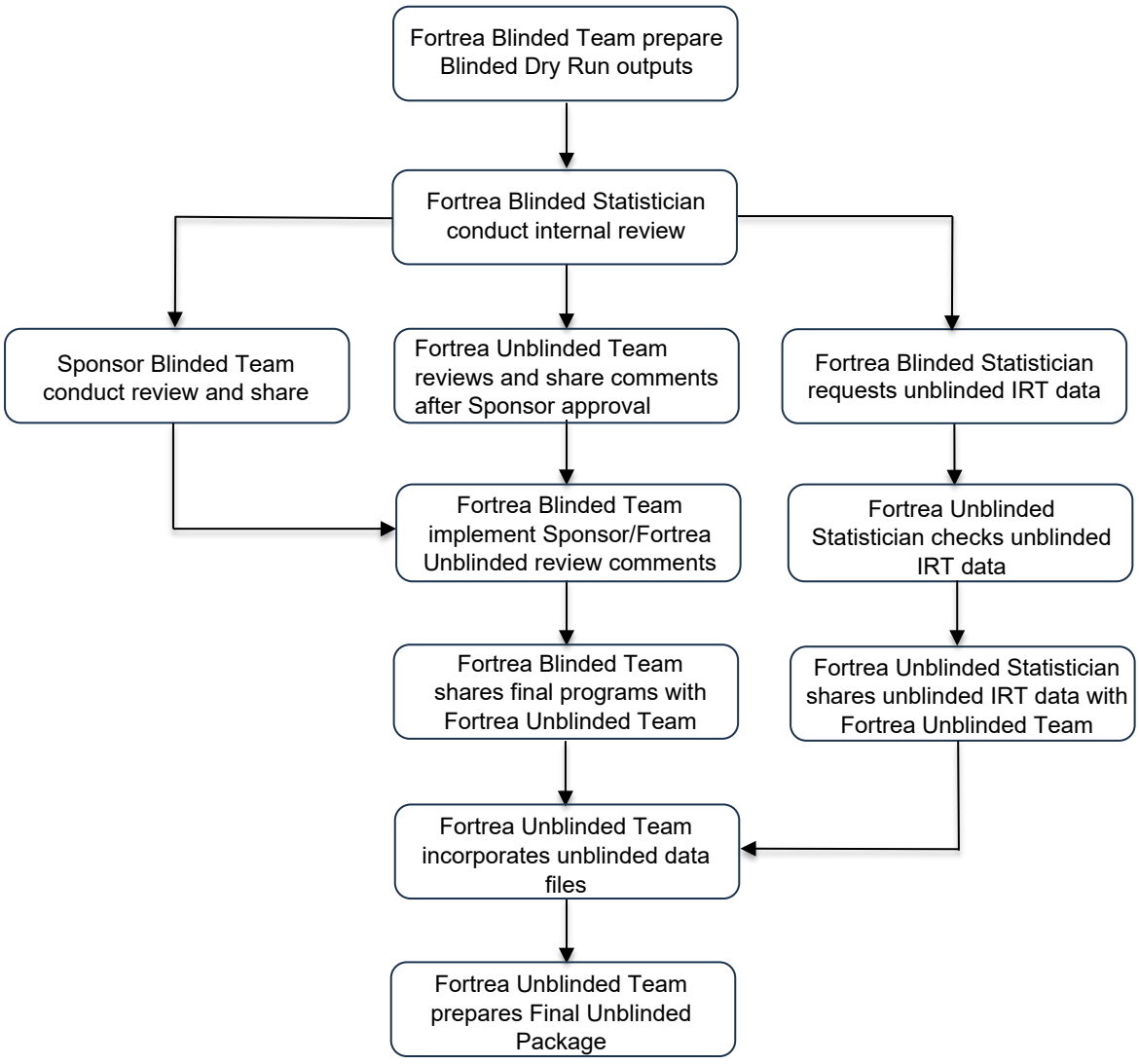

Fig. 3 - Overview of Communication and Role Responsibilities Between Fortrea's Blinded and Unblinded Teams During Interim Analysis in Blinded Clinical Trials

SYSTEM CONSIDERATIONS

When both blinded and unblinded teams operate within the same programming environment, to facilitate seamless execution of the shared programs, the folder structures for blinded and unblinded areas are designed to be identical, ensuring consistent program and library paths.

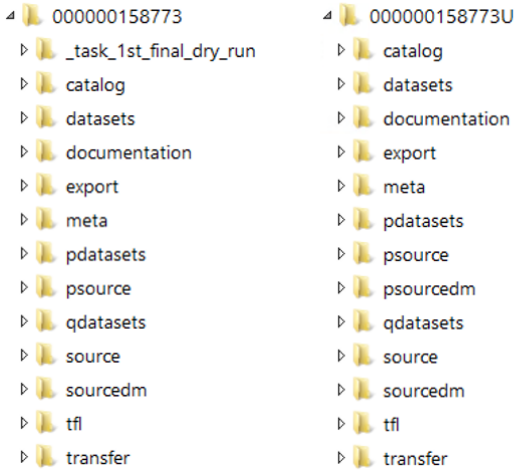

Fig.4 - Access-Controlled Folder Structure for Blinded Studies: Separate Blinded and Unblinded Areas with 'U' Prefix for Unblinded Data

While this setup enhances operational efficiency, it also introduces potential risks, such as inadvertently accessing or executing programs in the wrong location. To mitigate these risks, it is essential to implement the following precautions:

- Restrict access to unblinded study folders, ensuring that only authorized unblinded personnel can read and write their contents.
- Ensure that unblinded personnel do not accidentally place any unblinding information into blinded study folders.

At Fortrea, we are familiar with two main approaches to managing access rights. In one approach, all study folders are accessible to all users by default, with specific locations restricted to the unblinded team. In the other, users are granted access only to folders that correspond to their specific roles, ensuring that blinded and unblinded teams operate within clearly defined boundaries. While both approaches effectively protect unblinded folders, the second method offers an additional layer of system-level prevention against cross-contamination of the blinded area. Under the first approach, Unblinded Statistical Programmers must exercise caution when program reference paths that point to blinded locations, as running such programs could inadvertently overwrite files in blinded folders.

When sending unblinded data transfers to the sponsor, it is critically important to use a secure, restricted connection and to ensure the files are delivered to designated restricted-access folders on the sponsor's side.

COMMUNICATION AND DOCUMENTATION IS KEY

Effective communication between blinded and unblinded teams is essential to maintaining trial integrity, especially when both teams operate within the same organization. While shared infrastructure and proximity can offer operational efficiencies, they also increase the risk of accidental unblinding due to miscommunication or unclear handovers

Structured and well-governed communication is therefore essential to:

- Ensure program integrity by allowing the blinded team to maintain full ownership of programs.
- Enable safe troubleshooting when unblinded data reveals issues that require program adjustments.
- Avoid indirect unblinding signals, such as missing data records, unexpected file structures, or comments that hint at treatment allocation.

BEST PRACTISE

Clear Role Separation

- Define and document the responsibilities of blinded and unblinded teams, ensuring that only the blinded team maintains and updates programs

Consider Blinding Plan Document

In addition to SOPs, some sponsors utilize a Blinding Plan document to formally outline the blinding strategy across the study lifecycle. This document typically includes:

- A detailed description of which teams are blinded and unblinded.
- Specific data elements considered potentially unblinding.
- Procedures for handling unblinded data transfers.
- Communication escalation process.

Although not universally adopted across all partnerships, the Blinding Plan serves as a valuable tool for ensuring clarity and accountability.

Controlled Handover Process

- The blinded team may create a user guide-style document outlining the programming setup, execution order, and instructions for referencing unblinded data sources.

- Observed findings during unblinded execution are documented in logs and communicated without revealing data content.

Audit Trails and Access Logs

- All communications and file exchanges are version-controlled and logged to ensure traceability.

Training and SOPs

- Teams are trained in blinding principles, and SOPs are in place to guide interactions between blinded and unblinded personnel

CONCLUSIONS

Sponsors may look to set up blinded and unblinded teams within separate companies to ensure full separation. However, many unexpected unblinding risks still apply whether these teams are in the same or different companies. If full data access separation by independent teams within the same organization can be achieved, clinical trials can benefit from a range of operational and strategic advantages by fostering collaboration between those blinded and unblinded teams. Internal teams typically communicate more efficiently than when external vendors are additionally involved, which helps reduce delays in program development, troubleshooting, and data handovers. Challenges encountered during unblinded program execution, such as unexpected data formats or missing values, can be swiftly addressed through direct communication. Shared infrastructure and coding conventions ensure that programs developed by the blinded team are compatible with execution by the unblinded team. Blinded and unblinded folders can mirror each other, allowing seamless program execution while maintaining strict data segregation. Consistent programming standards further minimize the risk of misalignment in data structures, naming conventions, and output formats. This integrated approach also accelerates turnaround times for interim analyses by eliminating the need for external contracting, onboarding, and data transfer logistics. Internal teams can rapidly conduct dry runs, validations, and final executions. Centralized documentation, audit trails, and SOPs enhance transparency and accountability, while CAPA processes and regulatory compliance monitoring become more streamlined. Moreover, internal teams can quickly adapt to protocol amendments, data anomalies, or sponsor requests, reducing dependency on external timelines and contractual constraints.

However, despite these advantages, the risk of accidental unblinding remains if communication is not carefully managed. Effective and disciplined communication between blinded and unblinded teams is not merely a procedural requirement, it is a fundamental component of trial integrity.

To support this integrated model and mitigate risks, training is essential, in addition to highly controlled data access. Ensuring that all team members understand the boundaries, workflows, and safeguards involved in blinded-unblinded collaboration is critical to maintaining trial integrity. Training documentation should outline best practices, and communication protocols, helping teams navigate the complexities of working across blinded and unblinded environments. By embedding training into the operational framework, we reinforce consistency, reduce errors, and uphold the highest standards of data integrity and regulatory compliance.

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ACKNOWLEDGMENTS

We would like to express our sincere gratitude to Yan Spivak for providing valuable input and for taking the time to review the internal documentation developed to support this process, and Nicky Lawrence for detailed review and insightful suggestions.

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