



Clinical and Regulatory Master Plan

FOCUS. EXPERTISE. QUALITY.

Agenda



- Introduction
- Master Plan
- Conclusion and Take Home Message

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- Joined Premier Research in January 2009
- Employed as a Project Manager/Product technical specialist for BSI Healthcare Division working with CE-mark process for Class III medical devices
- Extensive experience with European regulatory system

Efraim Roe Kozorovitsky, B.EMS, MBA



- Joined in 2005 and oversees Clinical Operations for medical devices
- Background in Emergency Care Medicine
- More than 10 years of accumulated experience conducting clinical investigations and working with CE-mark process for all types of medical devices including active implantable devices

About Premier Research



- Full-service, Top 15 Global CRO with Dedicated Medical Devices Group Headquartered in Switzerland and Boston
- Primary Research Focus in Cardiovascular, Orthopedics, Neuroscience, Analgesia, Oncology, Infectious Disease, and Wealth of Experience in Pediatric Trials
- Excellent History of Repeat Business and Client Retention
- Consulting and Operational Excellence to Provide a Solutions Driven Approach to Clinical Research
- More than 1,100 Employees Operating in more than 30 Countries

Clinical Regulatory Master Plan

What is it?



- A business plan
- Includes:
 - Who are we (as a company)
 - What are we doing (our products)
 - Where are we now
 - What is our goal (where are we going to)
 - How are we going to get there (and how much will it cost)

Clinical Regulatory Master Plan



- Why do we need one?
 - to support of financial rounds (with potential investors)
 - to serve as status report to the company board
 - to negotiate with regulatory bodies for approval
 - as part of Design Dossier
 - to provide a clear vision to company and employees on the goals of the company
 - to continuously monitor actual versus plan

Clinical Regulatory Master Plan



- Written by
 - Project Leader

- With input from
 - Scientific Specialist
 - Biostatistics
 - R&D
 - Manufacturing
 - Marketing
 - Regulatory
 - Finance

Clinical Regulatory Master Plan



- Approved by
 - Sign off by all input parties
 - Approved by Executive Management

Master Plan

Contents



- Company description
- Device description
- Strategic plan (inc. Marketing)
- Scientific rationale for each indication or claim
- Validation plan and timelines for each indication

Master Plan

Contents - Clinical Trial Master Plan



- Manufacturing timelines per size/model
- Regulatory/Clinical strategy worldwide
- Clinical investigation planning and timelines, projected sample size for each investigation
- Resources – human and financial, yearly budget breakdown

Who we are

Company description



- Structure
- Investors
- Employees
- IPs
- Patents

What are we doing and Where are we now



Device description

A description of the Device (same as in design dossier):

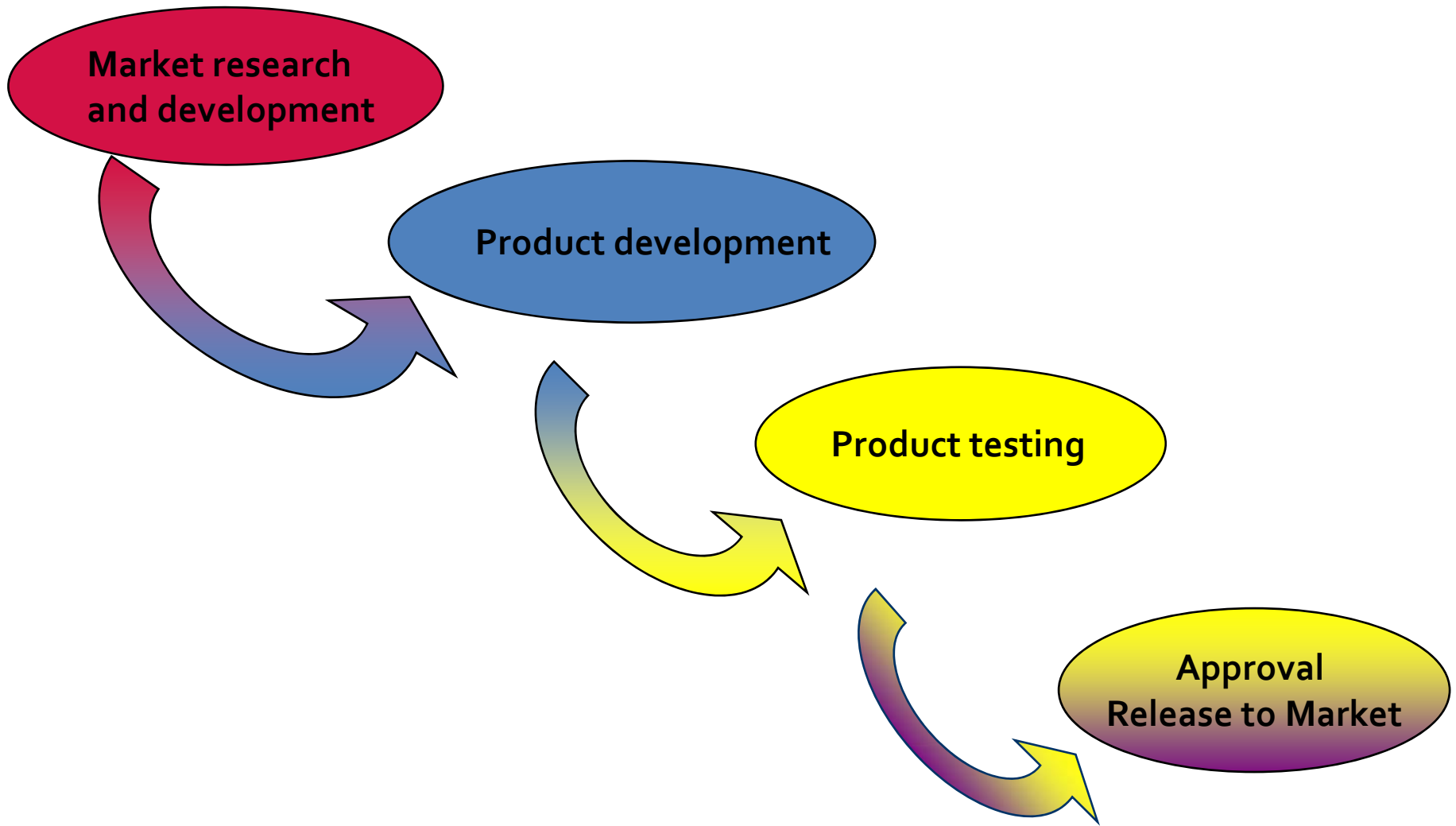
- Intended use
- Indication
- Tests performed
- Risks
- Compliance with essential requirements

* Each device requires its own section

** ER/IB/RA can be used as appendices

Where are we going to

Strategic plan



New Product



- Is the market interested in our new product?
 - Innovative?
 - Price attractive?



New Market



- Explain the driving force behind
 - Customer demand ?
 - Regulatory requirements ?
 - Governmental changes ?
 - Potential size of the market
 - Market growth
 - Cost of creating a new market.

Potential for Marketing



- Evaluate market potential
- Evaluate new product opportunities

Market Analysis



- Is there an existing market
- What's the market size
- What are the target markets
- Barriers for entering this market
- What's the growth potential
- Cost for entering that market

Strategic Planning



Design Input and
Feasibility



OK

Define market strategy and evaluate
market potential for each intended use

R&D engineering

Strategic Planning



Prototype



- Risk analysis
- Adjust product design and performance according to market feedback
- Pre-clinical studies i.e. biocomp., toxicity, bench testing, lab testing, packaging, sterility testing.

Strategic Planning



Clinical Investigation Master Plan



Pilot Study(ies)



- Define different intended uses if applicable in accordance with marketing plan
- Set up clinical strategy for each Intended use if significantly different

- User feedback and preliminary market feedback
- Preliminary safety performance and/or efficacy

Strategic Planning



Design Freeze



Performance/
Efficacy & Safety
Investigations

- Update risk analysis if appropriate
- Update investigator brochure
- Revise clinical master plan if needed

- Literature review
- Clinical investigation - 'investment'
- Publish clinical data
- Create marketing materials

Risks of going to market without clinical data?



- “Safety and performance/efficacy” may not be guaranteed
- Regulatory risk
- Marketing risk
 - Physicians will want proper data
 - Will set up their own clinical investigations
 - Result often in not significant conclusive data
 - Sponsor is not master of the play anymore and has no defense
- No added value to a start-up company, reduces power when negotiating exit

How will we get there



- Scientific rationale for each indication or claim
- Validation plan and timelines for each indication
- Manufacturing timelines per size/model
- Regulatory plan
- Clinical Plan
- Company resources plan

How will we get there

Scientific Rationale



Remember

- Each Indication or claim should be referred to separately.
- Each indication or claim needs to be rationalized through:
 - a. Literature review
 - b. Clinical study
 - c. by both

How will we get there

Validation plan



Preclinical Validation

- Mechanical testing: verification and validation
- Preclinical studies (tests carried out to demonstrate fulfillment of the essential requirements/principles defined in the regulatory model of each market)

Preclinical Studies



- Must be based on the review of essential requirements/principles and risk analysis
- Choice of laboratories is essential
- GLP, GMP must be considered

Preclinical Studies



Bio-compatibility

- For CE marking and FDA submissions
 - Raw materials need a certificate of biocompatibility which can usually be obtained from the manufacturer
 - Different materials combined even if they are all biocompatible, need to be retested in their combination use in addition to the individual biocompatibility certificates

Preclinical Studies



- Bio-burden during manufacturing, assembly and packaging
- Packaging validation
 - Needs to cover physical and sterility integrity over time
- Validation of sterilization and shelf life

Preclinical Studies



- Fatigue testing of all components
 - Number and duration of cycles depends on duration of use and amount of stress applied in humans
 - Other bench testing depending on type of product

- Electro-magnetic testing
 - Take into account different international electricity norms i.e. different voltage systems etc.

- Resistance testing, interference with environment
 - Use applicable standards
 - Take different circumstances of use into account

Preclinical Studies



- Other specific tests
 - For devices utilising animal or human tissue
 - For devices including software

Preclinical Studies



- Prepare planning using time-frames
- Do not under-estimate duration and complexity of such studies
- Review data regularly and update the risk analysis and ER matrix.
- Verify strategy with regulatory authorities at the right time...
- Use expert reviews
- Nearly all results need to be available before starting a clinical investigation

How will we get there

Regulatory Plan



Market Access Strategy

- Establish the markets to enter into and the marketing claims
- Review regulatory requirements for each market – consolidation and how to obtain approval
- Review the pricing and reimbursement issues – establish a plan and how to obtain approval

How will we get there

Regulatory Plan



Regulatory Requirements for individual markets

- Risk analysis
- Pre-clinical testing: Use of essential requirements/principles and harmonised standards
- Quality requirements
- Clinical data and study plans required
- Safety requirements
- Post market surveillance

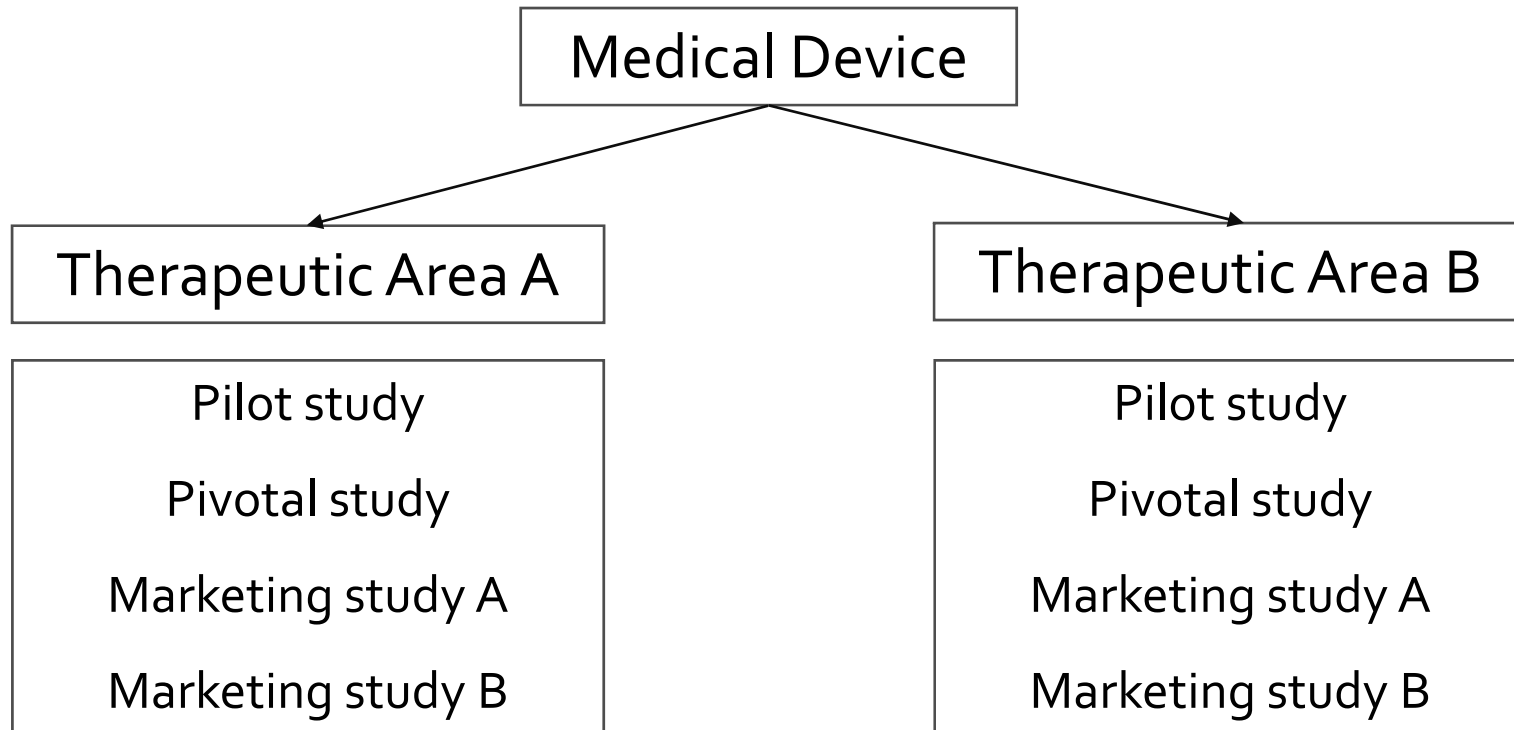
How will we get there

Clinical Investigation Planning

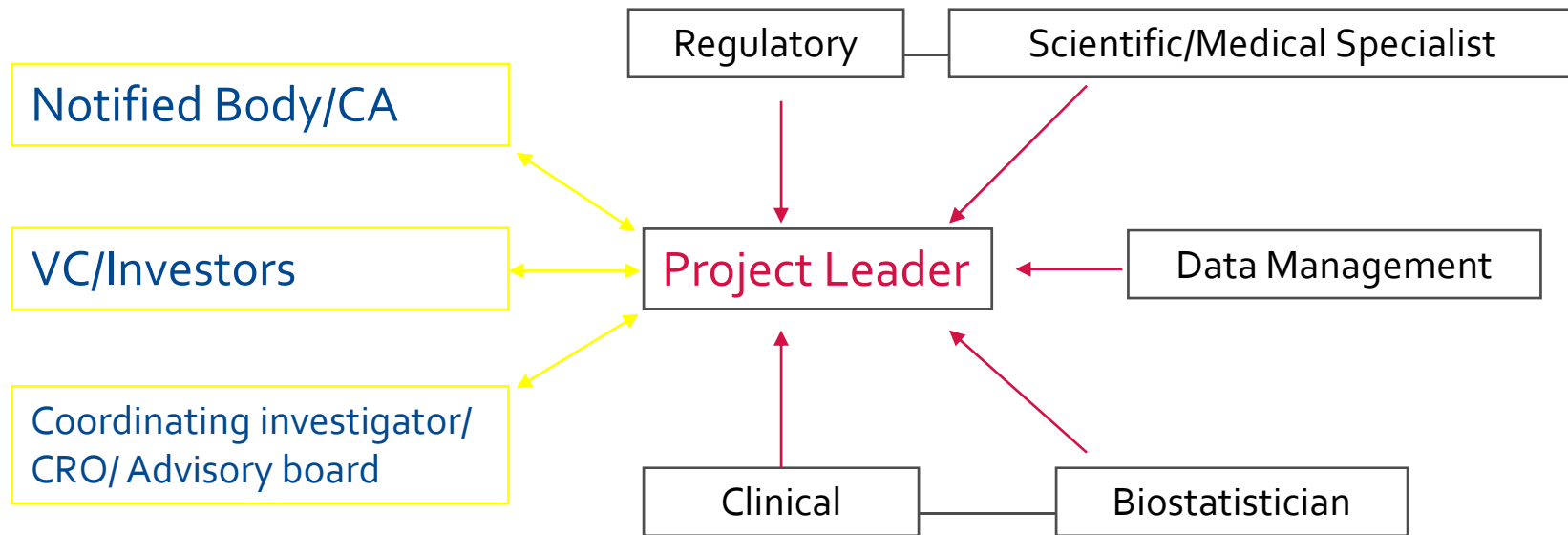


- Strategic planning
- Consequences of not conducting investigations
- Clinical development plan

Clinical Trial Plan



The Clinical Project Team



Which countries



Based on

- The regulatory strategy, where do you need regulatory clearance
- National regulatory constraints
- Market size
- Specific national requirements for reimbursement or post market surveillance.
- Key opinion leaders
- Medical practice in the different countries

Need for Clinical data



- Data for CE-mark
- Data for other regulatory approvals i.e. PMA, 510k, Japanese market access
- Marketing data
- Reimbursement data and clinical utility data
- Post market surveillance data

Performance vs Efficacy



- EU
 - Safety and Performance
- U.S.
 - Safety and Efficacy

Data for CE mark



Demonstrate Safety and Performance

- Critical literature review
- Prospective clinical investigations
- Or
- A combination of both

Data for CE mark



Critical literature review should be based on:

- Relevant data
 - Concerning significant identical technology
 - Concerning the same therapeutic indication

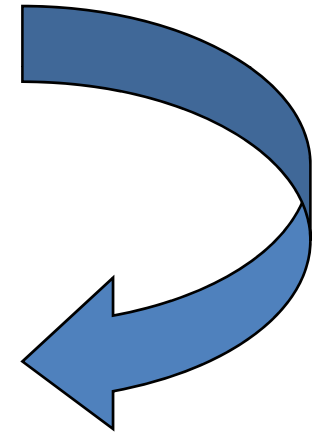
- Risk analysis including clinical risks in addition to technical risks
 - Cover all relevant points in the risk analysis with literature data

Data for CE mark



If safety and performance cannot be demonstrated in a significant manner with data from a critical literature review

Prospective clinical investigation is needed regardless the classification of your device



Methodology

Clinical Investigation Plan (CIP)



Objective

- Performance and safety for CE-mark
- Efficacy and clinical utility (reimbursement)
- Clearly outline the different objectives and ensure Performance is defined in the same way as will be in the CE-mark scope.
- Safety in relation to the risk analysis

Methodology

Clinical Investigation Plan (CIP)



- Make sure the objectives cover the claims and correspond with the endpoints of the CIP

Methodology

Clinical Investigation Plan (CIP)



Patient population

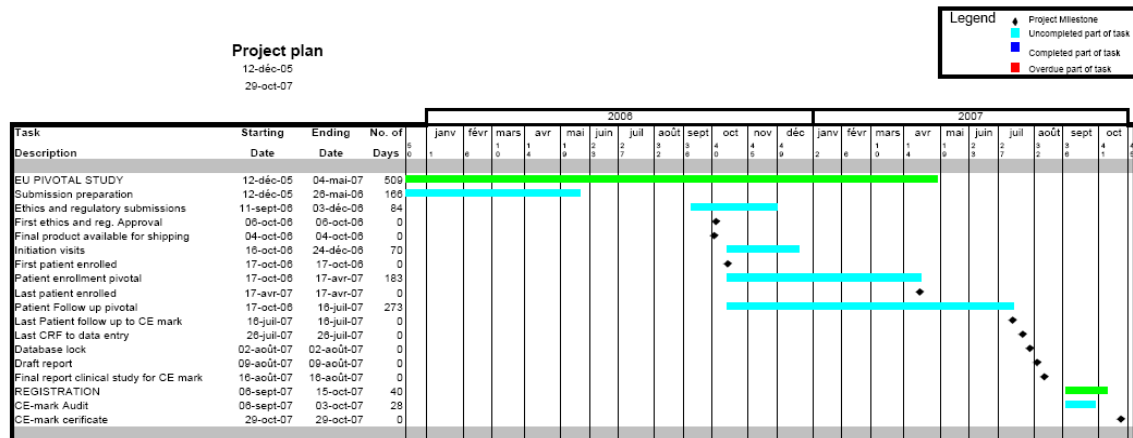
- Define how many patients – use statistical methods
- Define general eligibility criteria
- Define general enrollment process/rules

How will we get there

How much will it cost and how long will it take



- Estimated Budget
- Estimated Timelines (Use Gantt charts)



Keep in mind



- Check with notified body for EU trials to reach agreement on number of patients
- Rely on statistics only for FDA trials
- Set up SOPs, or rely on a third party who's quality system is compliant with both ISO 14155 parts 1 and 2 and 21CFR parts 50,56, and 812

Keep in mind



- Prepare pre-clinical file and maybe first human use experience, a clinical investigation plan and apply for an informal IDE meeting at the FDA



Keep in mind



- Discuss with the FDA the study design and objectives included in the protocol
- Get an agreement from the FDA on the amount of foreign data that they would accept

Keep in mind



- Write protocol objectives that cover both regulatory systems (if possible)
 - Earlier cutoff point for performance compared to efficacy
 - Let study continue to obtain FDA and marketing efficacy data
 - If possible also include clinical utility data for reimbursement

Keep in mind



- Good regulatory strategy = Good business strategy!
- Regulatory professionals should not only stick to the regulations, but also have a good business sense



Keep in mind



- Take into account regulations, marketing needs and business strategy of the company

Take Home Message



- Keep Global Approach for designing your clinical studies
- Good planning saves time and money
- Good Clinical and Regulatory Trial Master Plan serves as a vision to the company and aligns all company departments to one road

Premier Research

Clinical & Regulatory Medical Device Experts



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