SIOP PNET5 MB

EudraCT-Nr. 2011-004868-30

European study (16 countries) for children older than 3 to 5 years

Stratification according to clinical and biological criteria

- LR: Low-risk medulloblastoma (Phase II; Co-PI: F. Doz)
- SR: Standard-risk medulloblastoma (Phase III)

SIOP PNET5 MB: regulatory process and initiation

BfArM	21.11.2011	Submission Protocol V7
	13.01.2012	Approval V7
	29.05.2012	Submission Minor Specifications V8
	19.06.2012	Approval V8
Ethics Committee	22.11.2011	Initial submission
	31.10.2013	Approval (patient insurance pending)
	08.01.2014	Approval Amendment (V10)
Funding (DKKS)	14.09.2011	Funding application
	17.01.2014	Final confirmation of funding
UKE (Medigate)	since 2013	Start contracts with nat./internat. partners
German Cancer Soc.	06.08.2013	Assignment of Quality Label A
Insurance company	17.12.2013	Final Insurance Policy
UKE (Medigate)	07.04.2014	Initiation meeting Germany
	12.06.2014	Contract signed ZDM-GPOH (MARVIN)
	25.06.2014	Contract signed ZKS-Münster (consulting, SAE-management, monitoring)
	25.06.2014	Sponsor‘s permission to open study

Requirements for initiation in national groups I

- Contract on Sponsor delegations and Clinical Trial Agreement signed
- Confirmation (in contract) that “Consent for study participation and biological material transfer /analysis” allow link-anonymized data transferal to list of recipients
- Approvals from ethics committee/IRB and competent national authorities available (copy to coordinating investigator)
- Documented evidence of financing (incl. MARVIN) and insurance (please provide certificates)
- Set-up of adequate monitoring according to monitoring manual
- Nominate deputy national coordinator
- Notification about national requirements for SAE / SUSAR management
- Provide contact details of competent authorities, ethic commissions, recipients of SUSAR reports, sites, monitors…

Permission to initiate recruitment by coordinating investigator/sponsor

Requirements for initiation in national groups II

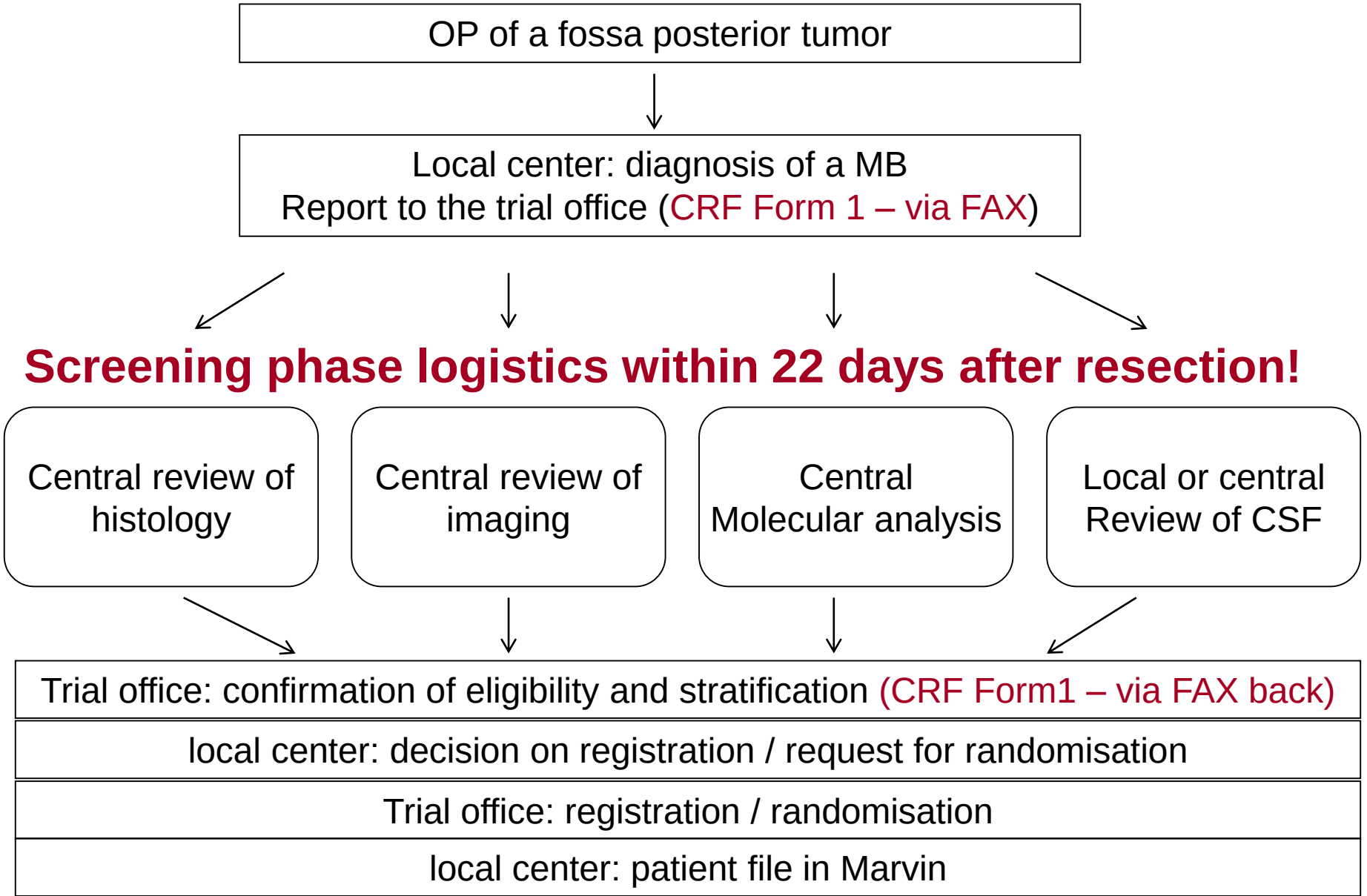
- Create investigator site files (table of contents for ISF provided by Hamburg team as template)
- Organise information pathways and documentation between sites and institutions (including histology/biology, radiology, RT-QC,…)
- Organise national initiation meetings with sites and provide copy of initiation documents (set of presentations for site training will be provided by Hamburg team)
- Organise MARVIN trainings
  (please provide list of MARVIN users incl. roles)

Responsibilities of national coordinator during the trial

- Decision about patients eligibility and inclusion
- Provision of all monitoring reports to sponsor
- Provision of semi-anually progress reports to sponsor (template provided)
- Keep contact lists up to date
- National query management
- SAE and SUSAR reporting

  (see training slides safety)

PNET 5 MB - Eligibility Phase



PNET 5 MB - Eligibility Phase

OP of a fossa posterior tumor

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Local center: diagnosis of a MB
Report to the trial office (CRF Form 1 – via FAX)

↙ ↓ ↓ ↘

Screening phase logistics within 22 days after resection!

Cer… …l …

Solution for data handling of preinclusion diagnostic to be solved nationally

Germany: Consent for eligibility evaluations

Tria… …k)

Trial office: registration / randomisation

local center: patient file in Marvin

RT quality control

Define roles, responsibilities, and logistics

<u>for timely, upfront RT QC</u> and documentation in each country

RT QC process in Germany:

- RT plan to be sent from local RT to national RT centre for review (DICOM);
  national RT centre sends QC and recommendations (letter) to local RT
- All RT CRF pages will be sent from local site to national RT centre for data entry in MARVIN
  ⟶ special role in MARVIN for RT

Documentation in MARVIN - roles

- Local documentation at sites in MARVIN possible (sites to be trained) or paper-based with central documentation at national centre (roles: site data manager and site investigator)
- National centre enters eligibility, results of central review of histology and radiology, results of CSF investigation, and molecular analysis (biology) = role of national coordinator
- Role RT quality control: For all RT documentation (in Germany carried out by national RT centre for review); can also be done at national centre
- Monitor role: to document monitoring in MARVIN

List of all MARVIN users required with assigned role(s) to be provided

Please note: Possibly more than one role per person necessary, e.g. if central documentation for different sites

Monitoring

- To be organized nationally according to monitoring manual
- The regular Monitoring visits are to be performed according the templates (see http://www.tmf-ev.de/Produkte/SOP.aspx;
- selection of hospitals to be monitored determined by the responsible National Coordinator
- Scope:

  One regular visit at minimum, second visit optional:

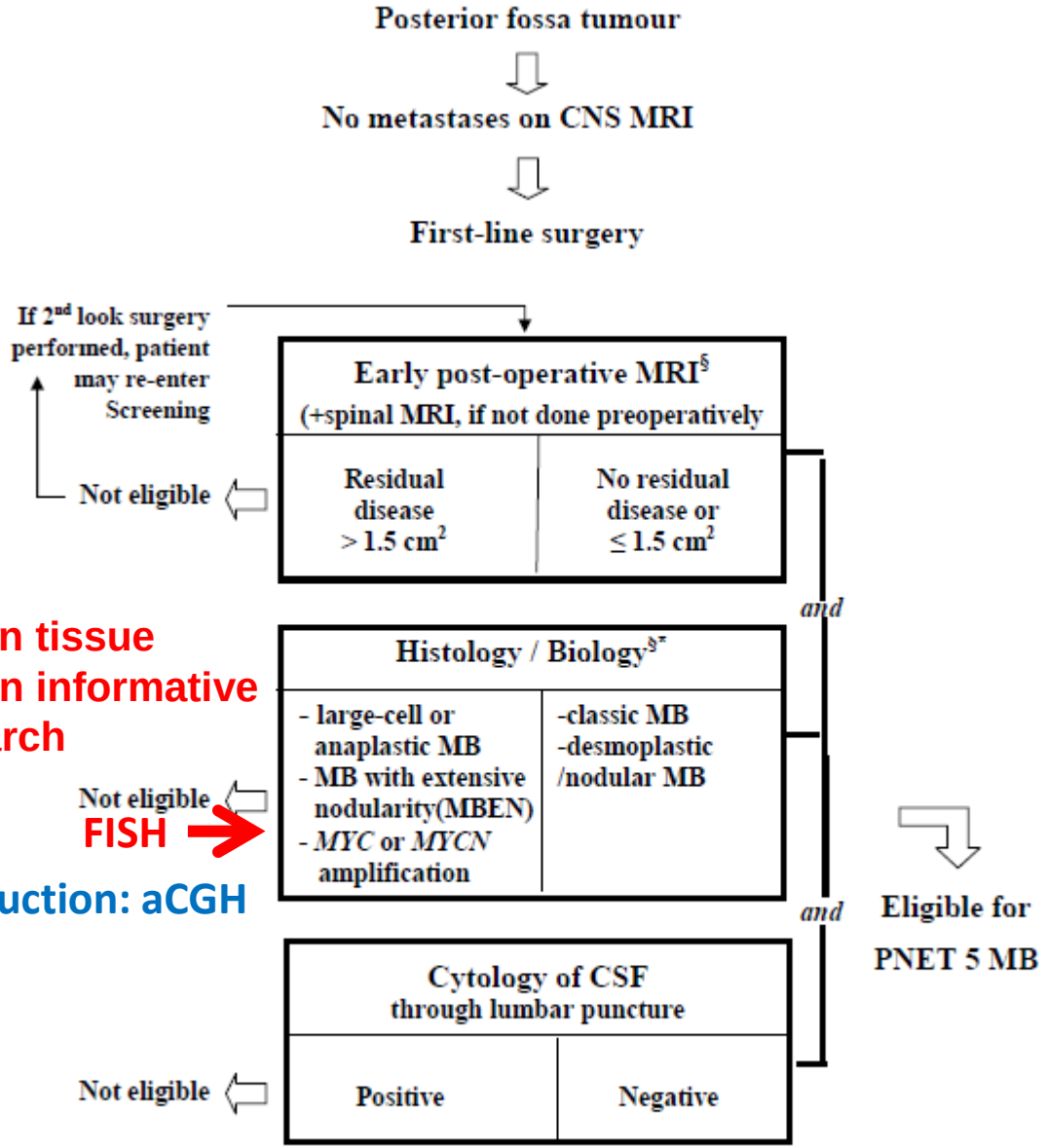
  In all institutions with 2 and more registered patients
  In institutions, reported by the national data centre as having poor compliance (poor or late documentation)
  10% of all other institutions chosen randomly.

  At least one visit per trial site should be planned for monitoring.

PNET 5 MB substantial amendment

- New definition WNT subgroup
  - ß-catenin mutation analysis mandatory
  - monosomy 6 analysis optional
  - WNT positive patients ≥ 16 years ⟶ PNET 5 MB-SR
- Reduction of CSI dose from 23.4 Gy to 18 Gy in PNET 5 MB-LR
- 40 days period for radiotherapy starts after 1st surgery, even if 2nd surgery was performed.
- Foreseeable inability to start RT within 40 days renders patients ineligible
- Particular per-protocol analysis in LR- arm excluding patients with RT > 40days
- Possibility to add new countries
- Implementation of study board and definition function of study committee
- Use of Health Tracker only for QoS assessments
- Minor changes as updated contact details, wording etc. included

PNET 5 MB substantial amendment

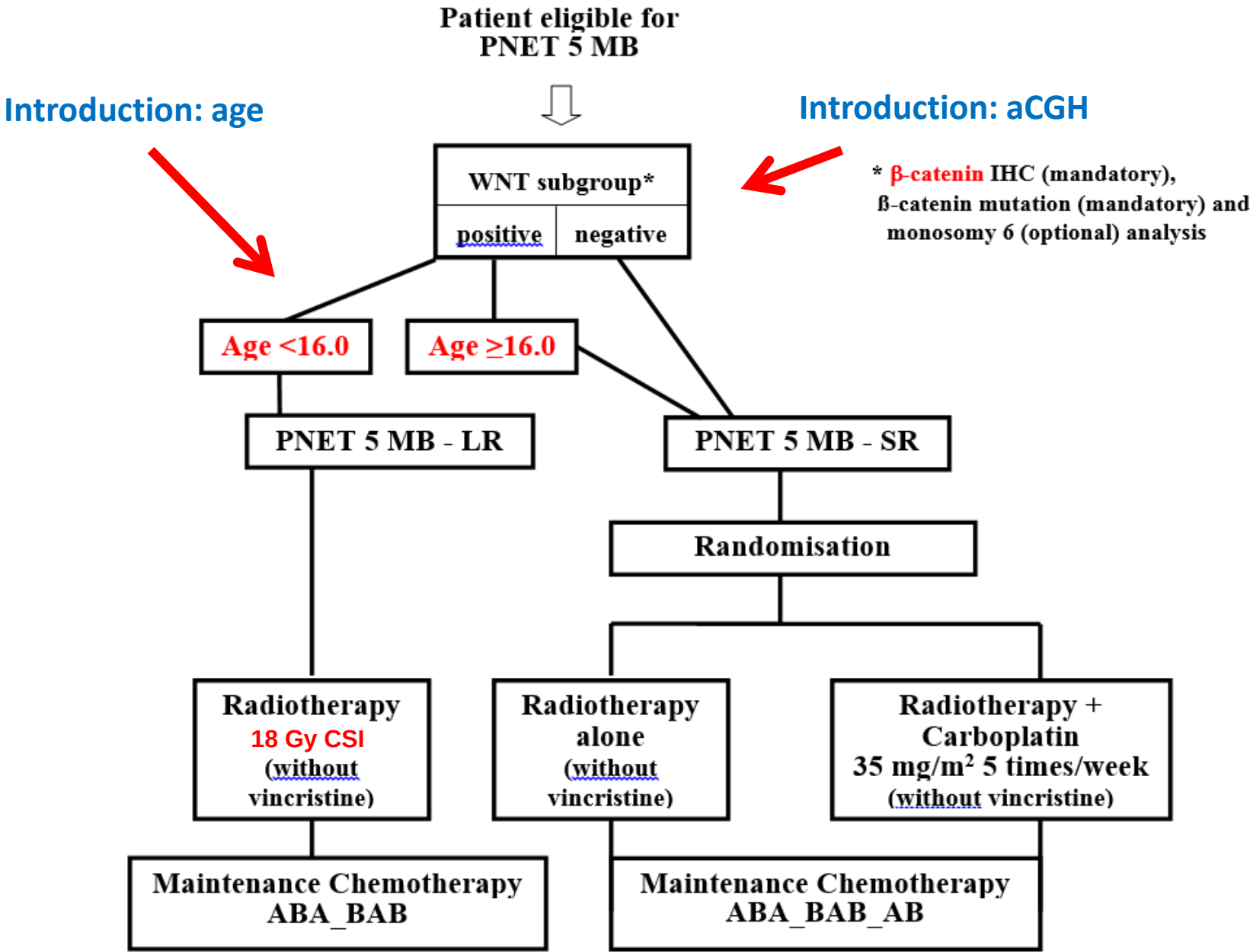


Mandatory frozen tissue

- **20% FFPE non informative**
- **Further research**

Introduction: aCGH

PNET 5 MB substantial amendment



PNET 5 MB substantial amendment

Timelines:

- Submission to leading ethic commission/IRB in Dec 2014
- Until approval, PNET 5 MB therapy to be conducted according to protocol version 10_21 Feb 2013

PNET 5 MB RT adherence phase

Two options suggested:

1. Include national groups who have implemented reference network
   - Confirmation that reference reviews conducted in compliance with protocol
   - Positive vote from PNET 5 MB discipline coordinators
   → participation possible after permission by sponsor

2. Use the new international HIT-MED registry for documentation of patients with medulloblastoma
   → registry not yet approved, start 01. Jan 2015

PNET 5 MB committees

- **Study board:** coordinating investigator, co-investigator, and discipline coordinators; the study board will oversee and monitor the progress of the study and make suggestions for amendments of the study protocol.
- **Study committee:** coordinating investigator, co-investigator, discipline coordinators, and national coordinator; the study committee will be informed about the progress of the study and approve protocol amendments.
- **Independent Data Monitoring and Safety Committee (DMSC):** 3 international experts to monitor the progress of the study from an ethical and scientific standpoint