

Recommendations for the Pre- Qualification Assessment in Human Abuse Potential Studies

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Draft Guidance on Pre-Qualification (PQ)

- Use of a pre-qualification phase is a common enrichment strategy to improve the power of the study to distinguish difference between treatments
- Section 2. Pre-qualification (PQ) Phase:

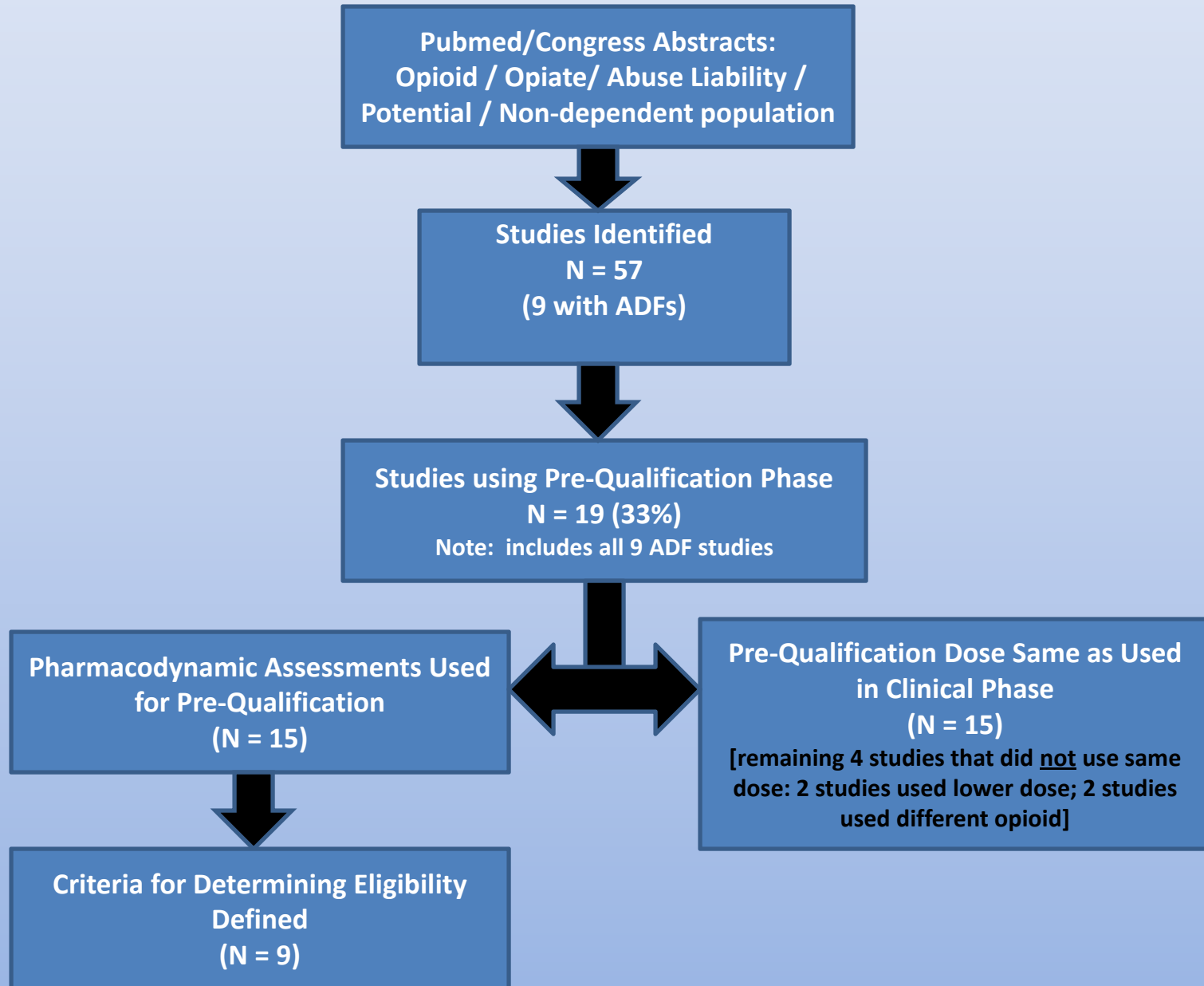
“The positive control should include a strength that is lower than or equal to the lowest strength selected for the assessment during the clinical phase. For example, a 15 mg dose of opioid could be used in the pre-qualification phase when a 30 mg dose will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, an acceptable response for the positive control should be chosen so that there is no overlap of responses. **For example, if a difference in drug liking scores between placebo and the positive control of 15 or higher is set and an acceptable placebo Emax response range is set between scores of 40 and 60 on a bipolar scale, liking scores for the positive control that successfully define a suitable subject for the treatment phase would be those equal to or higher than 75 on a bipolar drug liking scale.**

Background

- Appropriate choice of dose (lower vs. same) in the PQ phase has not been adequately compared and evaluated
- Appropriate PQ phase criteria for determining eligibility lacks consensus
- To explore this:
 - Literature review was conducted to survey use of a PQ phase in opioid abuse potential studies, including doses and criteria used
 - Analysis conducted to compare studies using a lower vs. same PQ dose on the sensitivity to detect treatment differences between active drugs and placebo

Literature Review Results



Literature Review Results (cont'd)

- Approx. a third of studies (11/38) without a PQ phase did not demonstrate significant differences between at least one active treatment and placebo (drug liking/high)
 - Many of the remaining studies did not provide data for pair-wise comparisons
 - Other methodological factors (e.g. population type) may contribute to these effects
- All studies assessing an ADF used a PQ phase. Most (8/9) demonstrated significant differences for all active treatments vs placebo; 1 study did not include placebo
 - Significant differences found despite variations in PQ criteria for determining eligibility

Literature Review Results (cont'd)

- Criteria for eligibility varied and not consistent
 - Seven studies noted numerical differences between peak effects (E_{max}) for active control and placebo; most commonly used was ≥ 15 point difference on bipolar Visual Analog Scales (VAS) (n=4)¹⁻⁴ and ≥ 20 point difference for unipolar VAS (n=2)⁵⁻⁶
 - Two studies defined acceptable placebo range of 0 or 50 (± 10 points) for unipolar and bipolar VAS, respectively^{2,3}
 - A minimum E_{max} (e.g. 75 suggested in guidance) for bipolar Drug Liking VAS not previously used
- Conclusions:
 - PQ phase can improve sensitivity and/or validity of testing and reduce variability in the data (McColl and Sellers 2006)
 - Further studies examining effects of different eligibility PQ criteria are warranted

Pre-Qualification Dose

- No published studies have compared the effects of testing lower vs. same doses in PQ phase; advantages/disadvantages of either approach are not well established

PQ Dose	Hypothetical Pros	Hypothetical Cons
Lower dose	May increase sensitivity of subjects to detect lower doses	May lead to plateau effects at higher doses due to response saturation/ poor tolerability
		May lead to increased dropouts in clinical phase (due to poor tolerability)
		May not be representative of population likely to tamper with opioid formulations (e.g. selects for a population of 'light' users)
Same dose	May mitigate plateau effects	May decrease sensitivity to detect lower doses since not established a priori
	May reduce dropouts since tolerability established	
	May be more relevant since this selects for a population using higher doses	

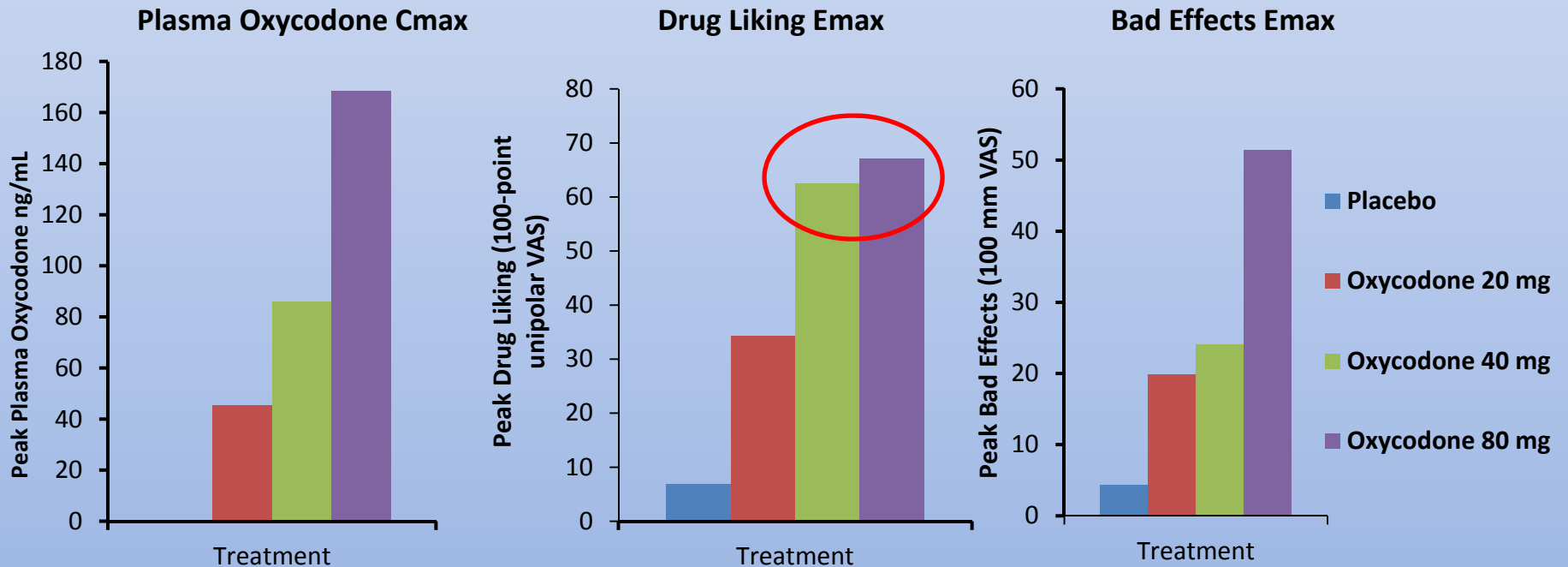
Comparison of Studies with Lower vs. Same Pre-Qualification (PQ) Dose

- Compared lack of ability of subjects to distinguish opioid from placebo (%) on peak Drug Liking VAS in studies with the same PQ dose vs. studies with lower PQ dose
- Results showed no differences between lower vs. same PQ doses in % of subjects who could not distinguish opioid from placebo

	Study	Investigational opioid ≤ 5 mm vs PLA	Active Control ≤ 5 mm vs PLA
Studies Using Lower Dose PQ	Webster et al., 2012a (oxycodone IR 40, 80 mg, po)	8/16 (50%)	2/16 (13%)
	Setnik et al., 2011 (oxycodone 20, 40 mg, po)	15/86 (17%)	4/86 (5%)
	Total	23/102 (23%)	6/102 (6%)
Studies Using Same Dose PQ	Webster et al., 2012b (oxycodone 40 mg, po)	6/46 (13%)	5/46 (11%)
	Study (oxycodone 60 mg, po)	6/26 (23%)	2/26 (8%)
	Setnik et al, 2013a (morphine 30 mg, IN)	9/27 (33%)	2/27 (7%)
	Setnik et al., 2013b (morphine 120 mg, po)	7/33 (21%)	1/33 (3%)
	Total	28/132 (21%)	10/132 (8%)

Plateau Effects

- Webster et al. 2012 study showed that although pharmacokinetic (PK) effects of increasing oxycodone doses (20, 40 and 80 mg) were linear, **Drug-liking** was non-linear beyond 40 mg;
 - oxycodone 40 and 80 mg showed saturation for Drug Liking VAS.
- Plateau effects may be related to tolerability i.e. peak *Bad Effects* VAS significantly increased for 80 mg (vs 40 and 20 mg) but not for 40 vs. 20 mg.



N=16

Plateau Effects (cont'd)

- 4 published studies: PQ dose was intermediate or highest of multiple doses studied
 - In all studies, the lower doses (i.e. lower than the PQ dose) significantly differentiated from placebo on measures of drug liking and high suggesting that this approach does not compromise sensitivity
- Pre-qualification with lower dose may lead to potential plateau effects with higher doses
 - Effects may be exacerbated if PQ criteria selects for subjects with extreme responses to lower dose
- Pre-qualification with lower dose may introduce decreased tolerability and/or saturation that may result in dampened subjective effects and risk false positive findings
- Additional studies are required to determine how PQ doses impact data

Concluding Remarks

- PQ phase can improve sensitivity and/or validity of testing and reduce variability in the data
- Use of same dose in PQ may have some advantages over use of a lower PQ dose
 - Lower PQ dose may result in plateau effects, increased dropouts and select for a less relevant population; should be considered carefully
- More research needed to establish appropriate eligibility criteria and dose selection

Discussion Points

1. Does the panel agree with the current draft guidance wording for the Pre-Qualification Phase?
 2. If not, what should be considered for PQ dose and eligibility criteria?
- Section 2. Pre-qualification Phase:

“The positive control should include a strength that is lower than or equal to the lowest strength selected for the assessment during the clinical phase. For example, a 15 mg dose of opioid could be used in the pre-qualification phase when a 30 mg dose will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, an acceptable response for the positive control should be chosen so that there is no overlap of responses. **For example, if a difference in drug liking scores between placebo and the positive control of 15 or higher is set and an acceptable placebo Emax response range is set between scores of 40 and 60 on a bipolar scale, liking scores for the positive control that successfully define a suitable subject for the treatment phase would be those equal to or higher than 75 on a bipolar drug liking scale.**

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