**UDS-based primary endpoints used to establish effectiveness for trials in opioid use disorder**

* RELAPSE: these outcomes seem to ignore what happens after the relapse
* Every relapse outcome requires a period of abstinence 🡪 Relapse and Abstinence outcomes are always linked (sine qua non) 🡪 can any relapse outcome be re-conceptualized as an abstinence outcome (or vice versa)?
* Reduction/non-abstinence (or “not necessarily abstinent”) outcomes can be measured independently of abstinence; reduction outcomes should be considered to account for what happens after a relapse, or to have a measurement for those who never fully achieve abstinence (and can therefore not relapse)
* Retention = non-dropout; is this a “higher-level” outcome? A certain retention (e.g., at least 4 weeks) in the trial is a pre-condition to measure UDS-based outcomes. Do we have to set a “minimum” time in treatment for other outcomes to “count” (e.g., opioid use based on only 1 measurement point is not very meaningful) or can retention be simply treated as a covariate?
* What about adherence? Is retention = adherence in the three CTN studies? A minimum adherence to the medication is a pre-requisite for the medication to take effect and to have an effect on UDS-based outcomes. Even in the absence of adherence, there can be variation in UDS-based outcomes (this is quite likely) but in this case, the UDS-based measures are no longer efficacy outcomes. Thus, the question arises how sensitive are UDS-based outcomes to the effect of treatment?
* Measurement frequency of UDS measures varies quite a bit between studies. But it’s the same for the 3 CTN studies (?)

Variables and studies in Table identified from (Biondi, Zheng, Frank, Petrakis, & Springer, 2020; Dennis et al., 2020).

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| **Primary Endpoint** | **Definition/Assessment of Outcome** | **Category** |
| Abstinence from heroin | Zero use (4 negative UDS, no missing) in the past 30 days | Abstinence (period) |
| Near Abstinence | <2 positive UDS | Abstinence (with “allowance” of pos. UDS) |
| % of participants continuously abstinent | Percentage of participants per treatment arm who maintained 12 consecutive negative UDS | Abstinence (continuous) |
| Slip/Occasional heroin use | <3 consecutive positive UDS (and no symptoms of withdrawal) | Abstinence (with “allowance” of pos. UDS) |
| Longest period of abstinence | Longest period of negative UDS between two positive UDS | Abstinence (period) |
| Complete Abstinence (Krupitsky et al., 2011)  (Rosenthal et al., 2016)  (Lofwall et al., 2018) | Krupitsky et al. (2011): No. of patients with confirmed opioid abstinence during weeks 5‐24, assessed by UDS (obtained weekly) and self‐report of nonuse (TLFB)  Rosenthal et al. (2016): Proportion of participants with no evidence of opioid use based on UDS (1×/month + at 4 random times for a total of 10 samples) and self‐report (TLFB)  Lofwall et al. (2018): Responder rate (no evidence of illicit opioid use via urine test result and self‐report‐TLFB used). Urine samples obtained at each study visit (weeks 1‐12, 16, 20, and 24) plus 3 random visits during weeks 12‐24. | Abstinence (complete) |
| Abstinence weeks (Krupitsky et al., 2011)  (Fiellin et al., 2006) | No. of confirmed opioid abstinence weeks, assessed by UDS (obtained weekly) and self‐report of nonuse (TLFB) | Abstinence (periods) |
| Relapse | 3 consecutive positive UDS | Relapse |
| Time to relapse (strict) | Number of days between baseline and occurrence of the first positive UDS | Relapse |
| Time to relapse (more lenient) | Days to 3 consecutive positive UDS | Relapse |
| % of participants in a drug free period | Time elapsed between the first day of naltrexone administration and the first evidence of use (positive UDS) | Relapse |
| Time to Opioid Use  (Lee et al., 2016)  (Mokri, Chawarski, Taherinakhost, & Schottenfeld, 2016)  (Lee et al., 2018)\* | Lee et al. (2016): Relapse Definition: ≥10 days of opioid use in a 28‐day period as assessed by self‐report (TLFB) or by UDS every 2 weeks; a positive or missing sample was computed as 5 days of opioid use  Mokri et al. (2016): Duration of verified initial opioid abstinence (self‐report via TLFB, days to first opioid‐positive or missed urine test, urine samples obtained 2×/week)  Lee et al. (2018): Participant has used non-protocol prescribed opioids starting at day 21 post-randomization as follows: 4 consecutive opioid use weeks OR 7 consecutive days of use by self-report. Use week: Any week during which a participant self-reports at least one day of non-prescribed opioid use, provides a urine sample positive for non-study opioids, or fails to provide a urine sample at the weekly assessment visit. | Relapse |
| Not-abstinent rate | Number of positive UDS divided by the number of weeks of study participation | Reduction/non-abstinent |
| Reduction of regular use | ≥50% negative UDS | Reduction/non-abstinent |
| Substantial Improvement (CTN-30) | Abstaining from opioids during the last week AND for at least 2 of the previous 3 weeks of the third month of BUP/NX treatment.  Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids). | Reduction/non-abstinent |
| % or no. of opioid-negative samples  (Ling et al., 2010)  (Mattick et al., 2003)  (Fiellin et al., 2006)  (Tanum et al., 2017)  (Haight et al., 2019)  (Lofwall et al., 2018)  (Strang et al., 2019)  (Woody et al., 2008) | Ling et al. (2010): Proportion of 48 urine samples (obtained 3×/week) negative for illicit opioids during weeks 1-16 of the trial  Mattick et al. (2003): The absence of morphine in urine samples (obtained randomly every 2 weeks)  Fiellin et al. (2006): Percentage of opioid negative urine tests (weekly)  Tanum et al. (2017): Proportion of opioid negative UDS (weekly) during study  Haight et al. (2019): Percentage of each participant's negative urine samples (obtained weekly) and self-reports of illicit opioid use from week 5 to week 24 [the authors call this outcome “participants' percentage abstinence from opioid use”]  Lofwall et al. (2018): Proportion of UDS negative for illicit opioids. Urine samples obtained at each study visit (weeks 1‐12, 16, 20, and 24) plus 3 random visits during weeks 12‐24.  Strang et al. (2019): Proportion of heroin‐negative UDS (obtained 3×/week) at the end of the 12‐week postrandomization time point  Woody et al. (2008): Percentage of participants with opioid‐positive urine test results at weeks 4, 8, 12 | Reduction |

*Note.* Negative UDS: opioid-negative Urine Drug Screen

\*Reported primary outcomes are proportion of participants who relapsed per treatment group + length of relapse free time per group.

Example of a very convoluted primary outcome (Wang et al., 2019): Treatment failure (3 consecutive opioid‐positive urine tests, dropout, discontinuation or discharge from study, or use of ancillary medication treatment for severe withdrawal over 3 days following randomization)

* The more OR statements, the broader/less specific the outcome, and – presumably – the easier to see a “treatment effect”.