The Patient Benefit and Public Health Benefit of Arm-Acquiring in Platform Clinical Trials

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Costs in New Treatment Development

- Time: very long (decades) due to
  - ▷ understanding of the disease
  - ▷ biological/chemical/technological development
  - ▷ administrative burden of several clinical trials
  - ▷ logistical burden of several clinical trials
  - ▷ patient recruitment in several clinical trials
- Money:
  - ▷ huge investment ($ billions)
  - ▷ very high risk of not reaching market (no revenue)

Clinical Trials

- Part of development are clinical trials (CTs)
- Typically two treatments: control (standard of care) and novel (not approved yet)
- Is the novel better than the control?
  - ▷ clinically relevant treatment effect difference
  - ▷ if not enough evidence, it will not be approved!

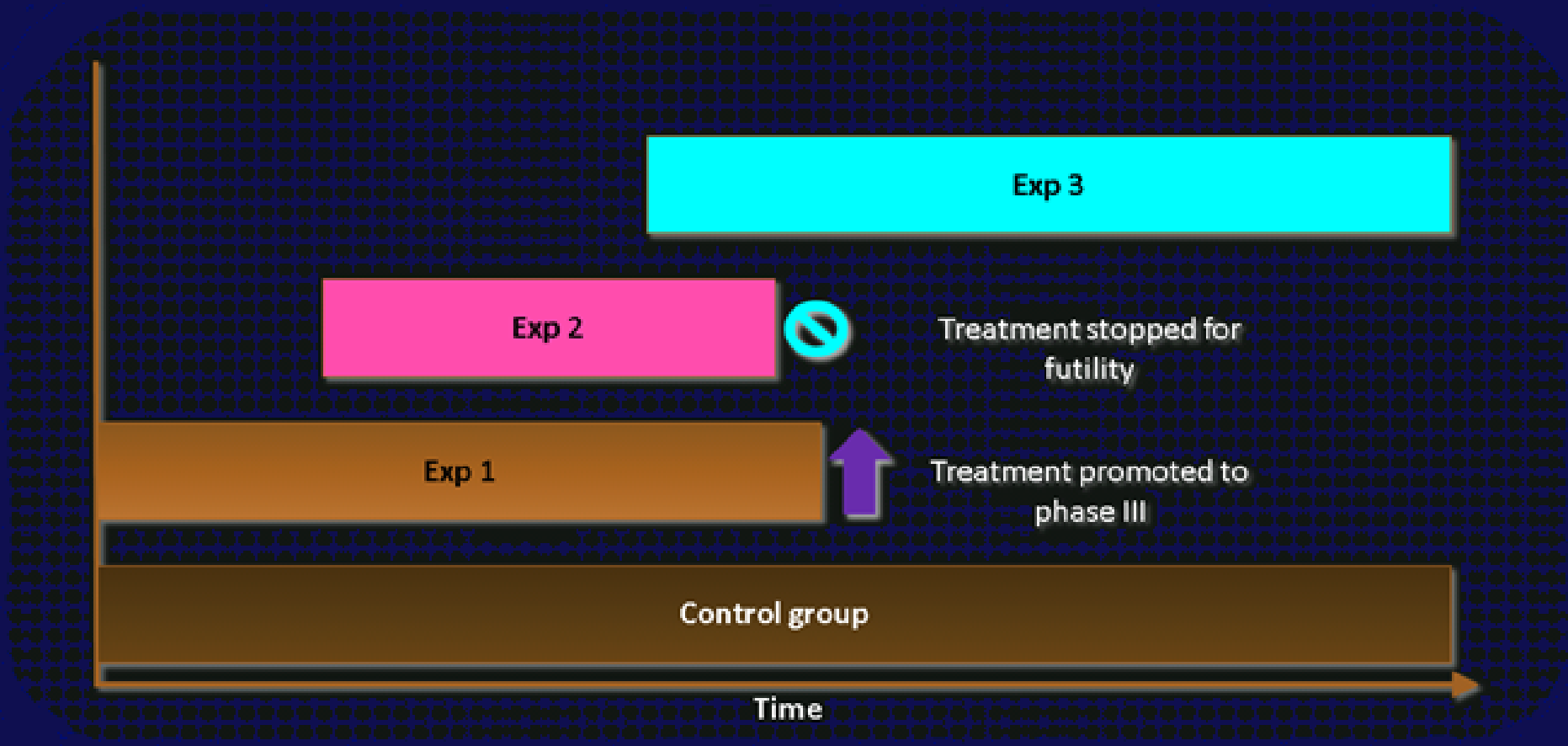
Patient and Public Health Benefit

- Using any CT, health benefit is decreased:
  - ▷ if the novel is better than the control:
    - — if is approved: unavailable to out-of-trial population until approved
    - — if fails CT: unavailable to out-of-trial population
  - ▷ if the novel is the same as the control:
    - — if is approved: no benefit, no harm
    - — if fails CT: no benefit, no harm
  - ▷ if the novel is worse than the control:
    - — if fails CT: harming in-trial patients
    - — if is approved: harming the whole population

Randomised Controlled Trial (RCT)

- The gold standard design: randomised controlled trial
  - 50% vs 50% fixed equal randomisation
  - diminishes some biases
  - in use since 1948 (advocated since Hill 1937)
  - its main goal is to learn about treatment efficacy with a goal of healing future out-of-trial population
  - assuming an infinite population — unrealistic!
    - there are $\sim$8 billion humans in the world
    - rare diseases affect hundreds/thousands
    - trials in paediatrics are smaller than RCT requires
    - trial recruitment is challenging for chronic diseases
    - very likely new treatments will appear in future

Platform Clinical Trials



Our Question

- To understand arm-acquiring in platform clinical trials
  - these can add in new treatments as become available
  - can be finite or perpetual
- Is the patient and public health benefit increased?
- We take the most optimistic approach
  - fully sequential allocation
  - immediate responses
  - complete controllability
- Relaxing any of these assumptions will, in expectation, lead to lower health benefit

Health Benefit Approach

- Important because healing the patients is the ultimate goal of new treatment development
- Bayesian decision-theoretic randomization
  - ▷ optimally solving learning/healing trade-off
  - ▷ both learning and healing takes place during the trial
  - ▷ a kind of response-adaptive design, see e.g.
    - Thompson (Biometrika 1933)
    - Glazebrook (Biometrika 1978)
    - Gittins & Jones (Biometrika 1979)
    - Armitage (ISR 1985)
    - Cheng, Su & Berry (Biometrika 2003)
    - Berry (Nature 2006), Cheng & Berry (Biometrika 2007)
    - Villar, Bowden & Wason (Statistical Science 2015)

UK Government Commitment

- to accelerate the use of adaptive trials, after the death of Dame Tessa Jowell on 12 May 2018, who said
  - "New adaptive trials can test many treatments at the same time. They speed up the process and save a lot of money."
  - "I am not afraid, but I am fearful that this new and important approach may be put into the 'too difficult' box."
  - "I hope this debate will give hope to other cancer patients like me, so that we can live well with cancer, not just be dying of it. All of us, for longer."

Our Bernoulli Model

- Binary treatment endpoints: success (1) or failure (0)
- Trial size: T patients
  - ▷ for how long the novel will be available
- Expected future out-of-trial population size: P
- K arms: arm k corresponds to treatment k
- Let $X_k(t)$ denote the (hypothetical) patient t's response from arm k. Then, $X_k(t) \sim \text{Bernoulli}(\theta_k)$ where θ_k is the unknown success probability of treatment k

Our Bayesian Approach

- Belief $\widehat{\theta}_k$ to be updated during the trial, as the expected value of its prior/posterior distribution
- Prior Distribution: Beta$(1,\ 1)$ (uninformative)
  - ▷ when arm k is first available in the trial
- Posterior Distribution: After observing s_k successes and f_k failures on treatment k, it is another Beta distribution (by conjugacy)

$$\text{Beta}(1 + s_k, 1 + f_k)$$

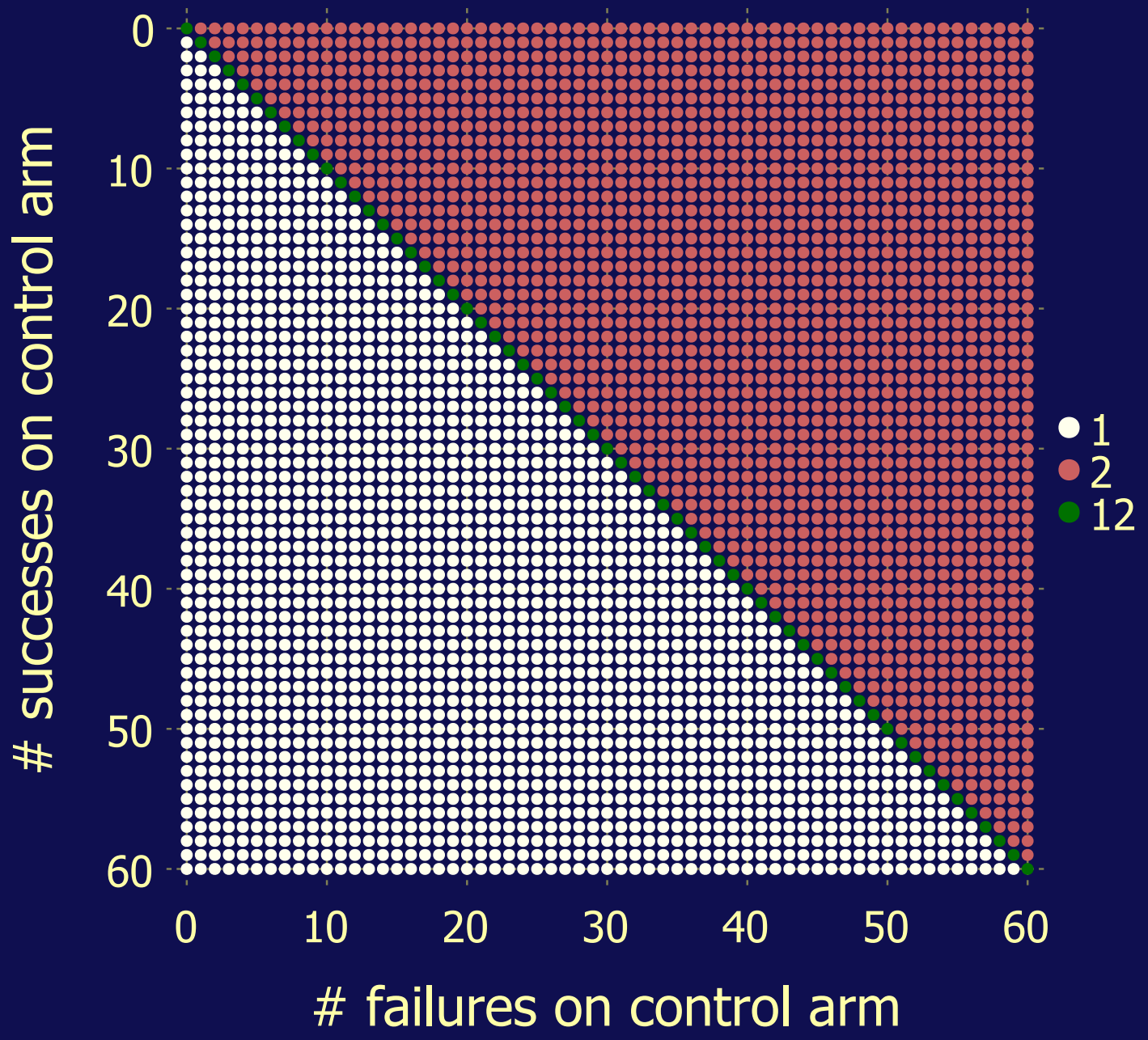
Optimal Health Benefit Design

- We assume out-of-trial population is treated with the treatment with higher MLE at the end of the trial
- We use dynamic programming to obtain an optimal response-adaptive randomization
  - ▷ optimal meaning providing the highest possible (expected) patient and public health benefit

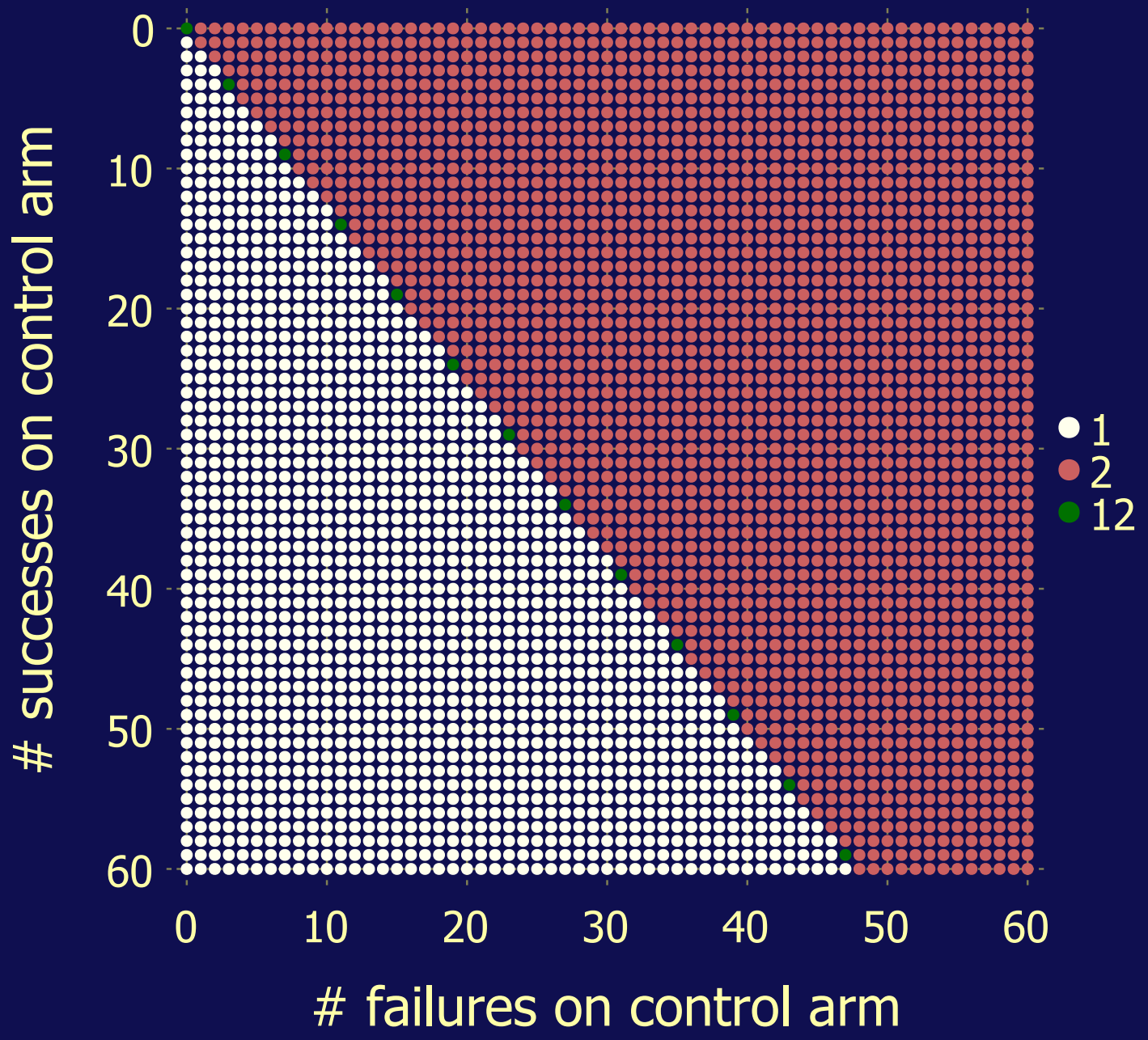
Introducing a Novel Arm

- We assume existing observations on the control arm
  - ▷ taking advantage of the platform trial design
- We present the following plots:
  - ▷ is the novel arm allocated to the first patient?
- Legend: control (1), novel (2), indifferent (12)

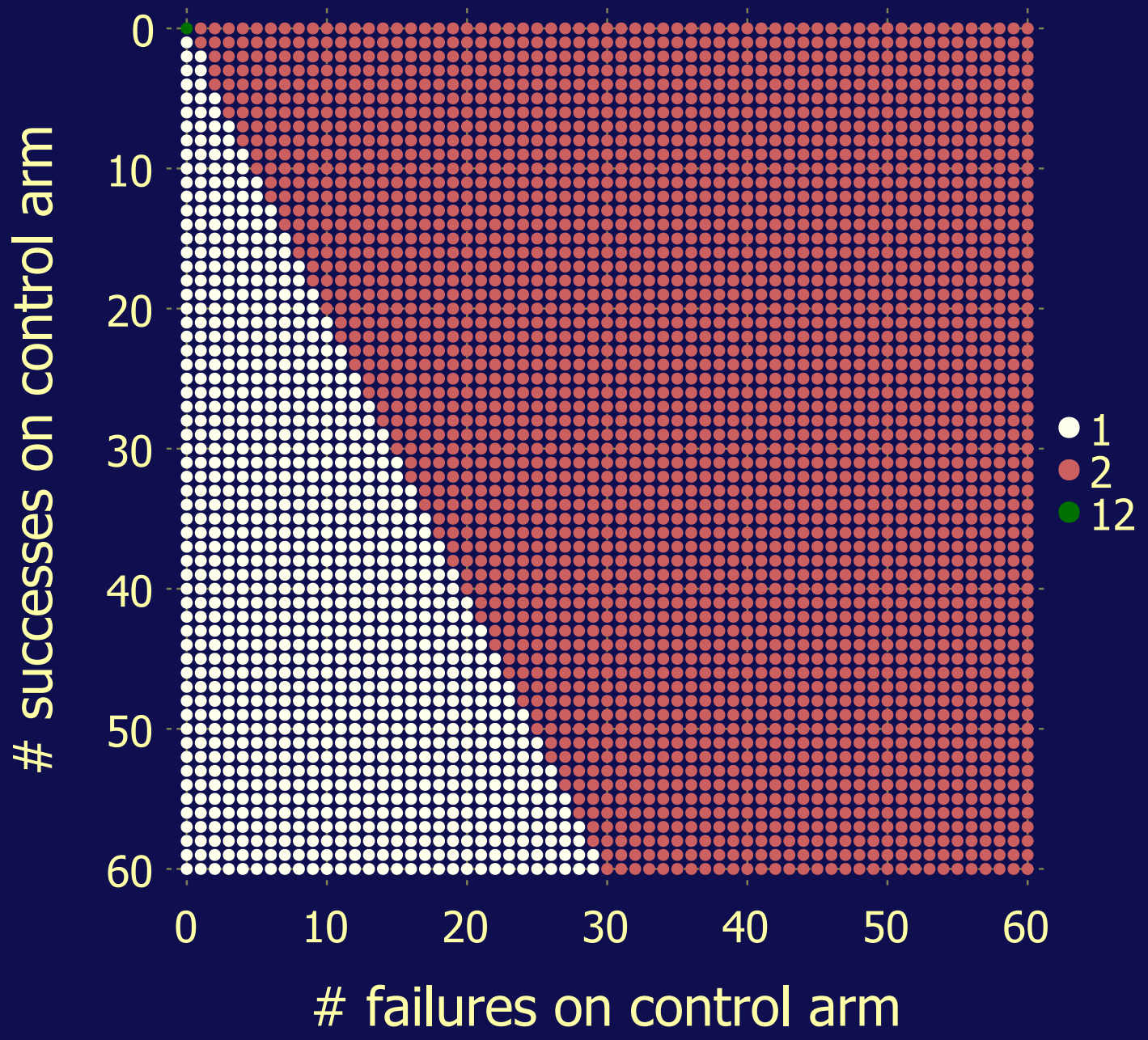
$T = 1, P = 0$: Optimal Allocation



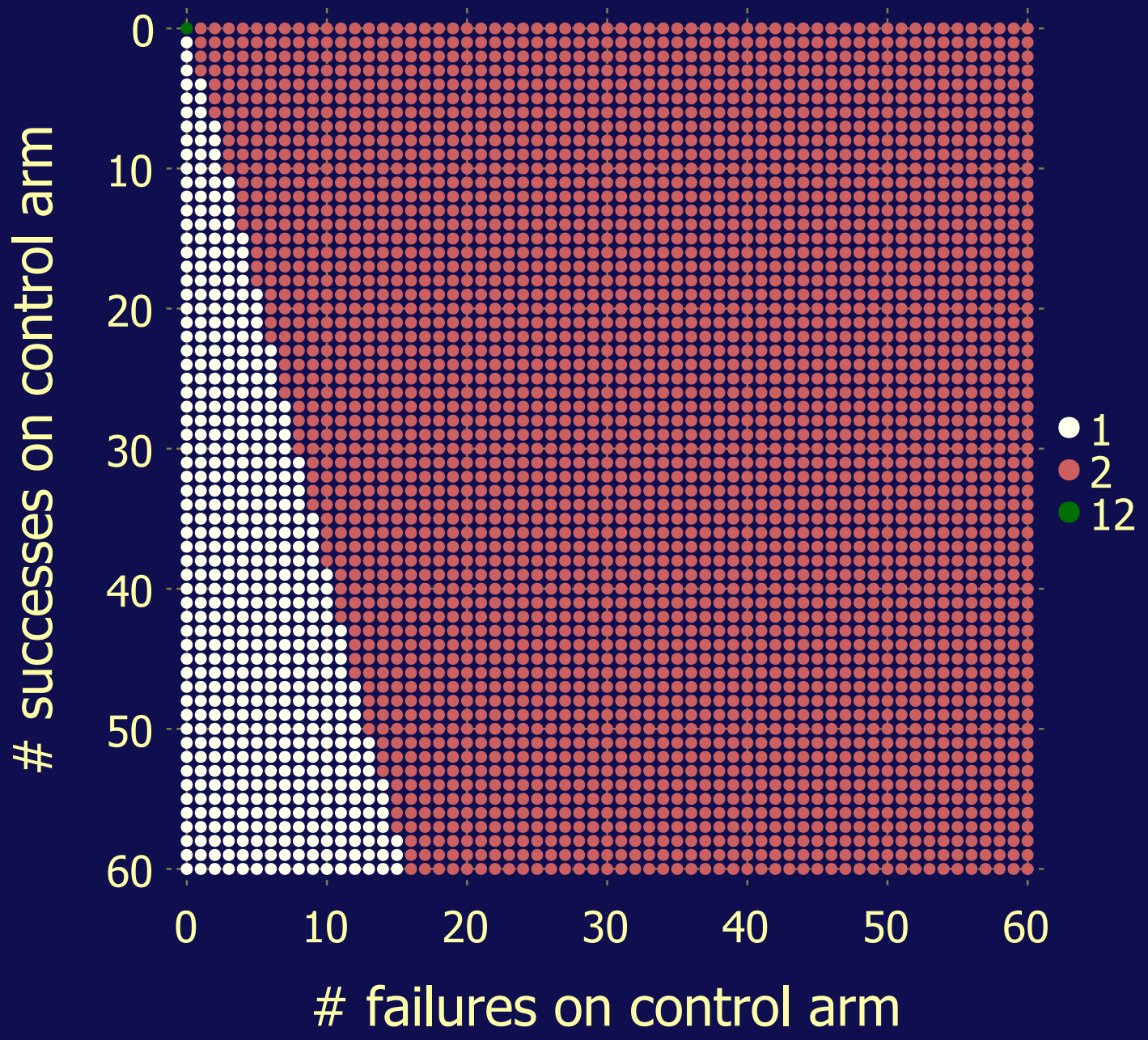
$T = 2, P = 0$: Optimal Allocation



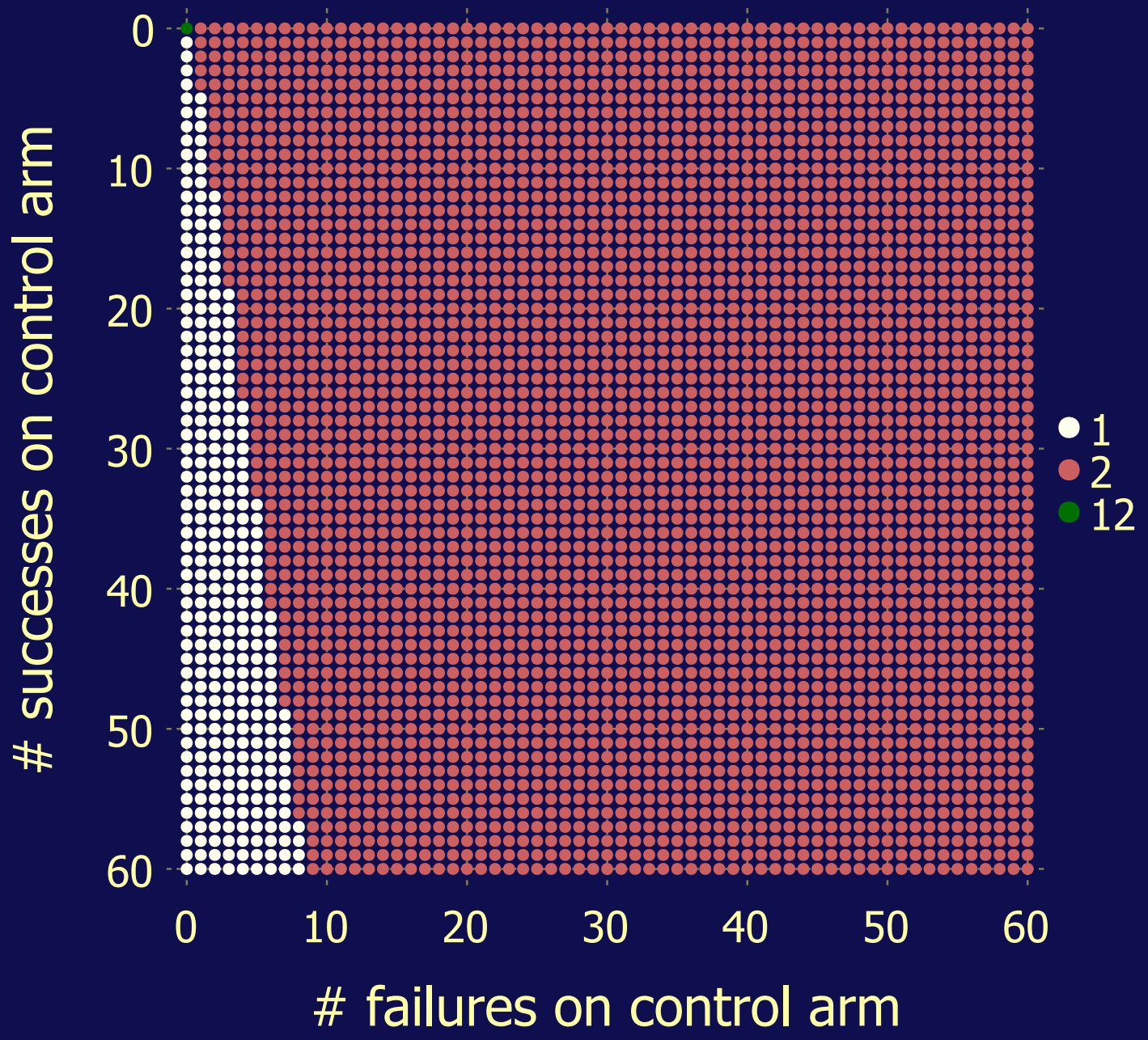
$T = 7, P = 0$: Optimal Allocation



$T = 30, P = 0$: Optimal Allocation



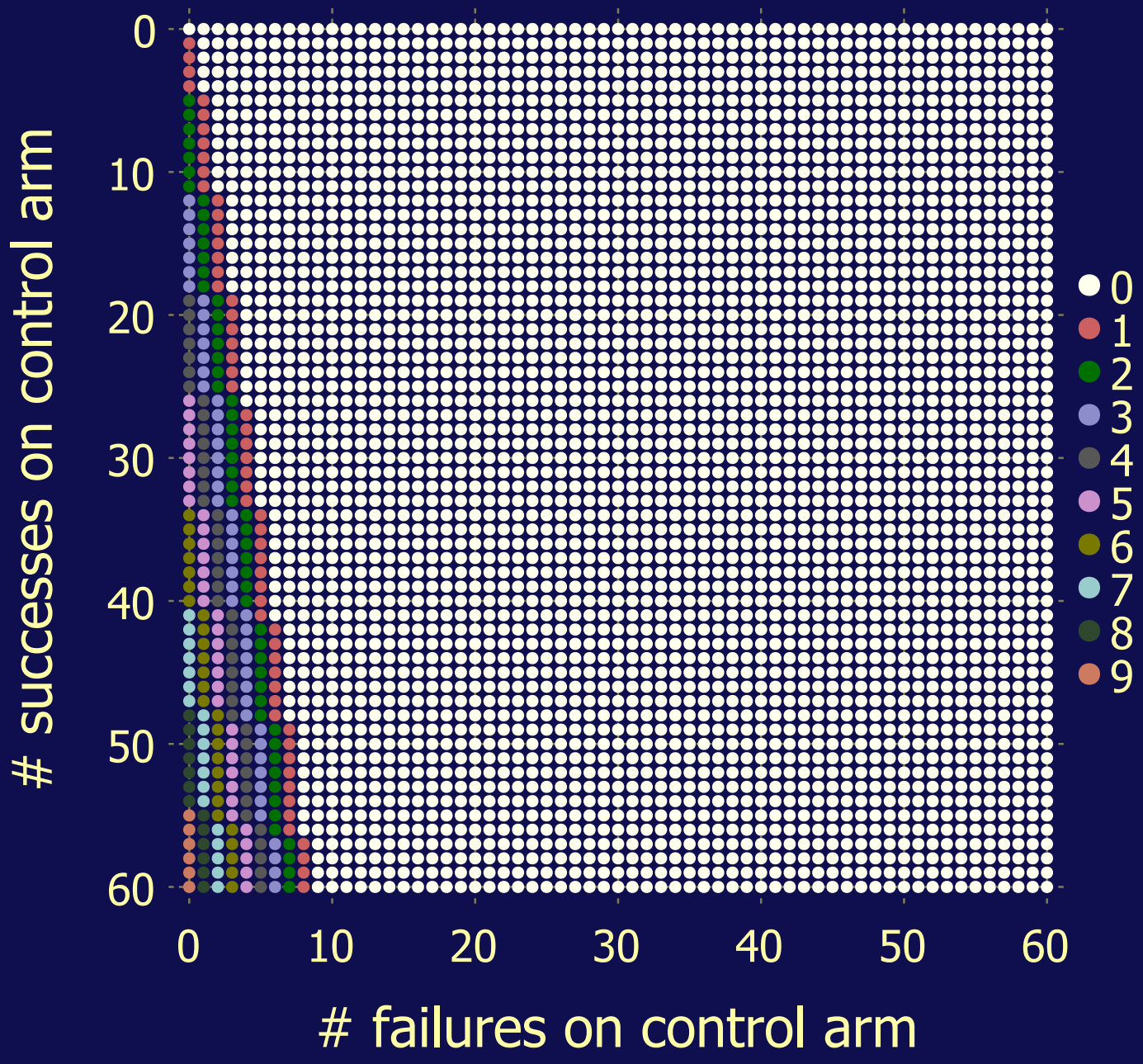
$T = 120, P = 0$: Optimal Allocation



Introducing a Novel Arm

- We present the following plot:
  - how many consecutive failures on the control do we need to allocate the novel?

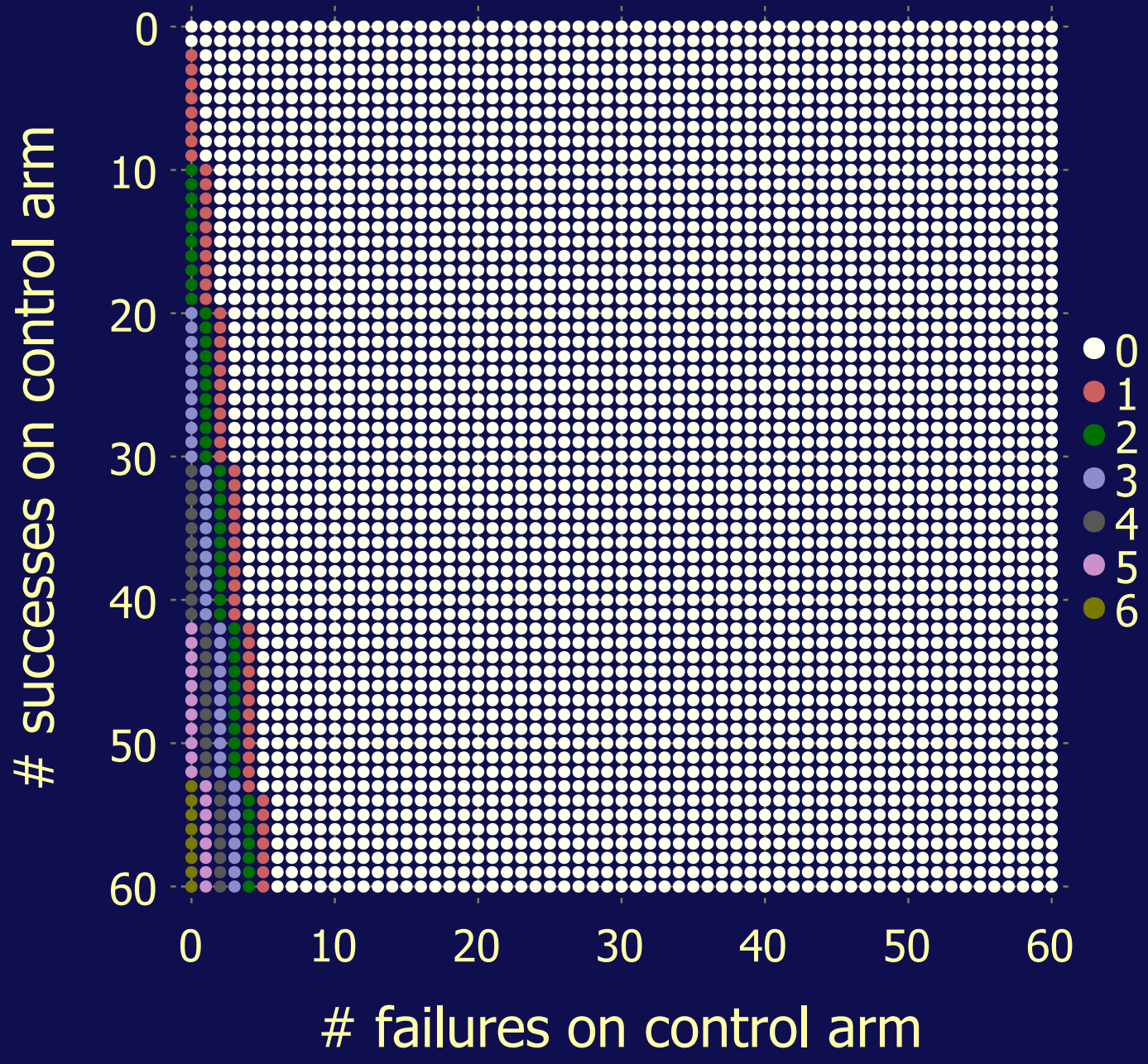
$T = 120, P = 0$: # Failures



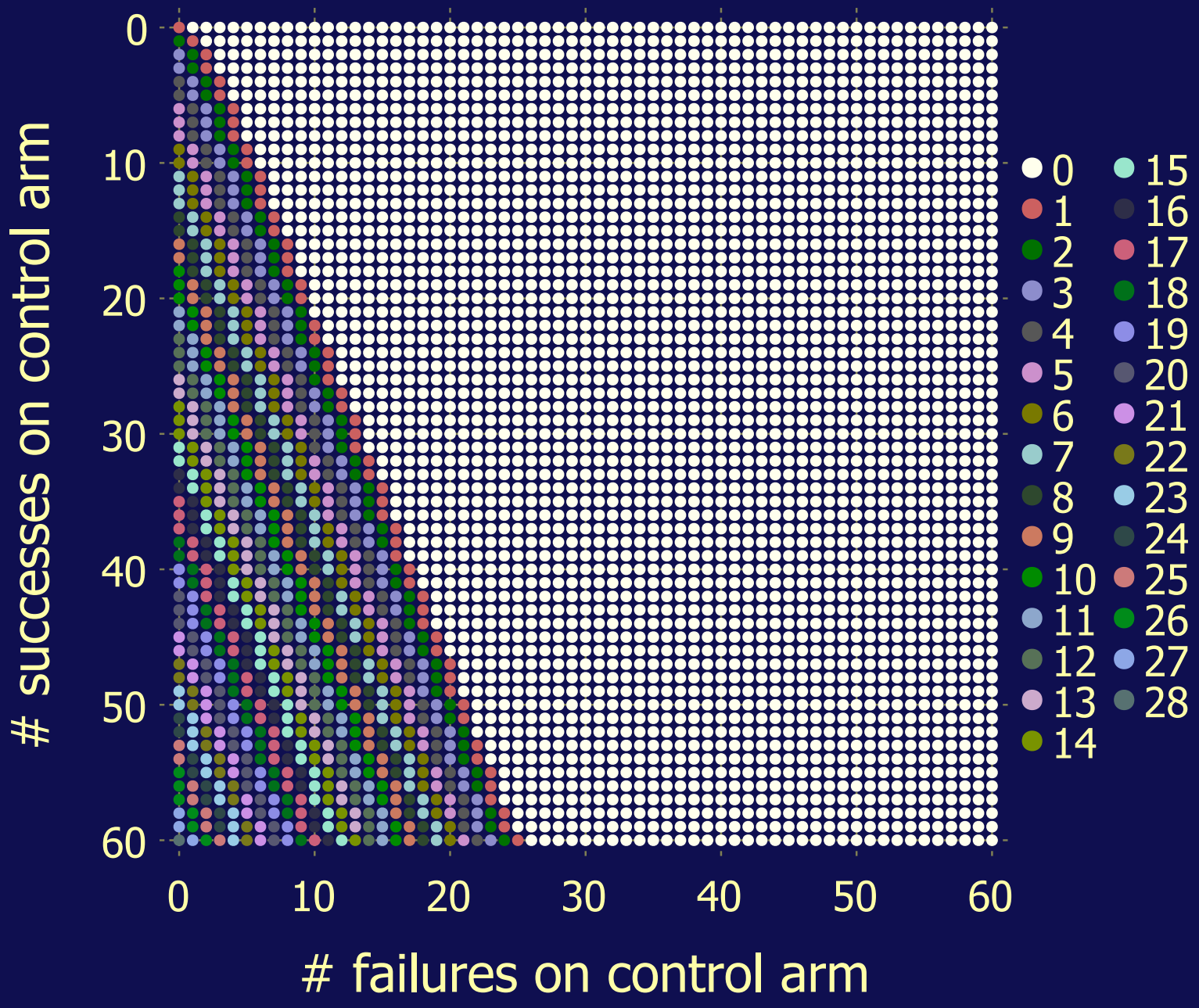
Introducing a Novel Arm

- We present the following plots:
  - ▷ if we force one patient on the novel and it is a success, how many consecutive failures on the control do we need to allocate the novel?
  - ▷ if we force one patient on the novel and it is a failure, how many consecutive failures on the control do we need to allocate the novel?

$T = 120, P = 0$: # Failures after Success



$T = 120, P = 0$: # Failures after Failure



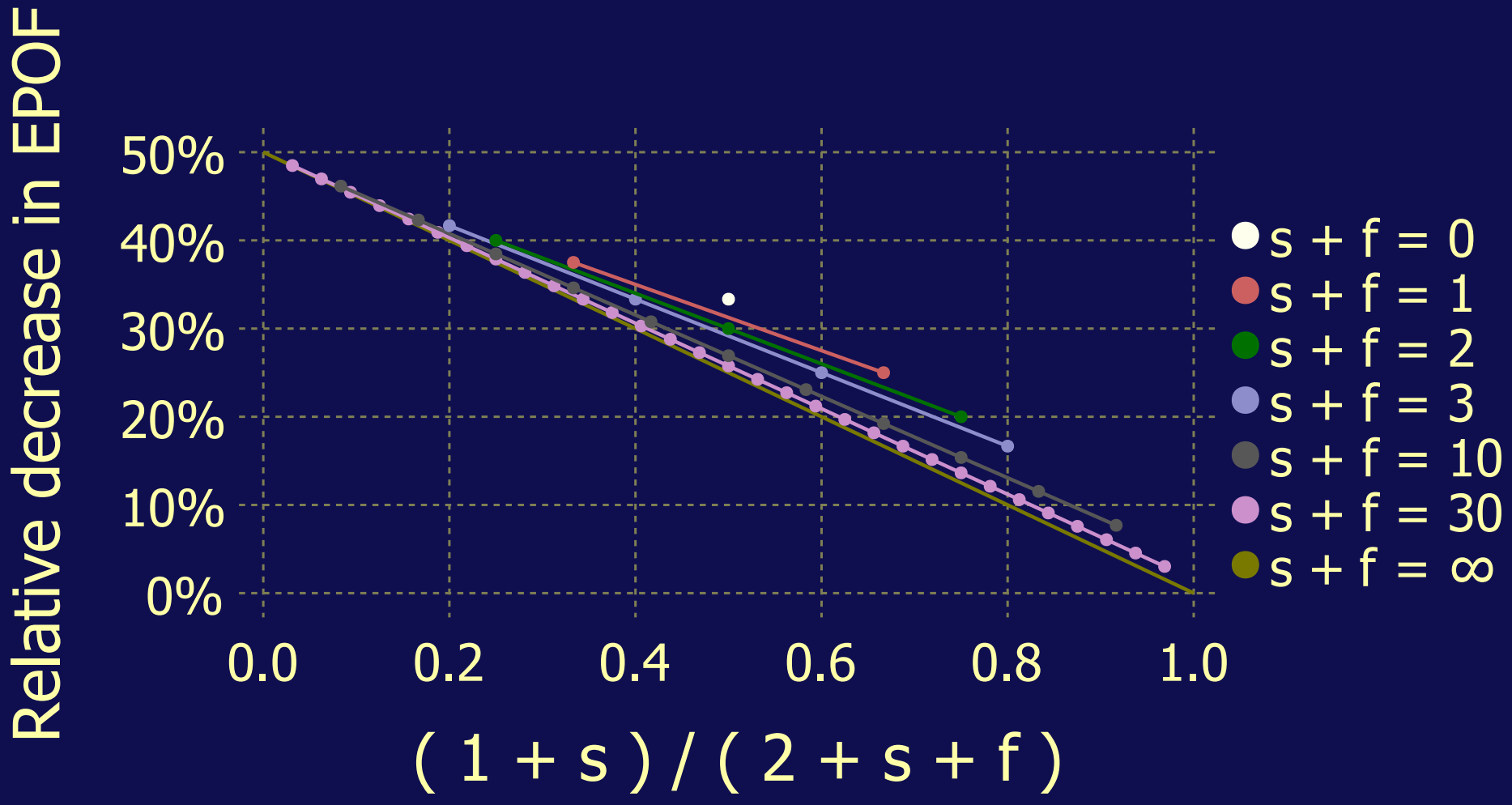
Perpetual Trials

- If $T = \infty$, trial allows for complete learning
  - ▷ we will correctly identify the best treatment
- Proposition: By adding in a novel arm in a trial with a control arm with observations s, f, the relative decrease in the expected proportion of observed failures (EPOF) is

$$\delta^{\text{EPOF}}(s, f) = \frac{1}{2} \cdot \frac{2 + f}{3 + s + f} \cdot 100\%$$

- If $s, f \to \infty$ in a way that $s/(s + f) \to \theta$, then $\delta^{\text{EPOF}}(s, f) \to (1 - \theta)50\%$

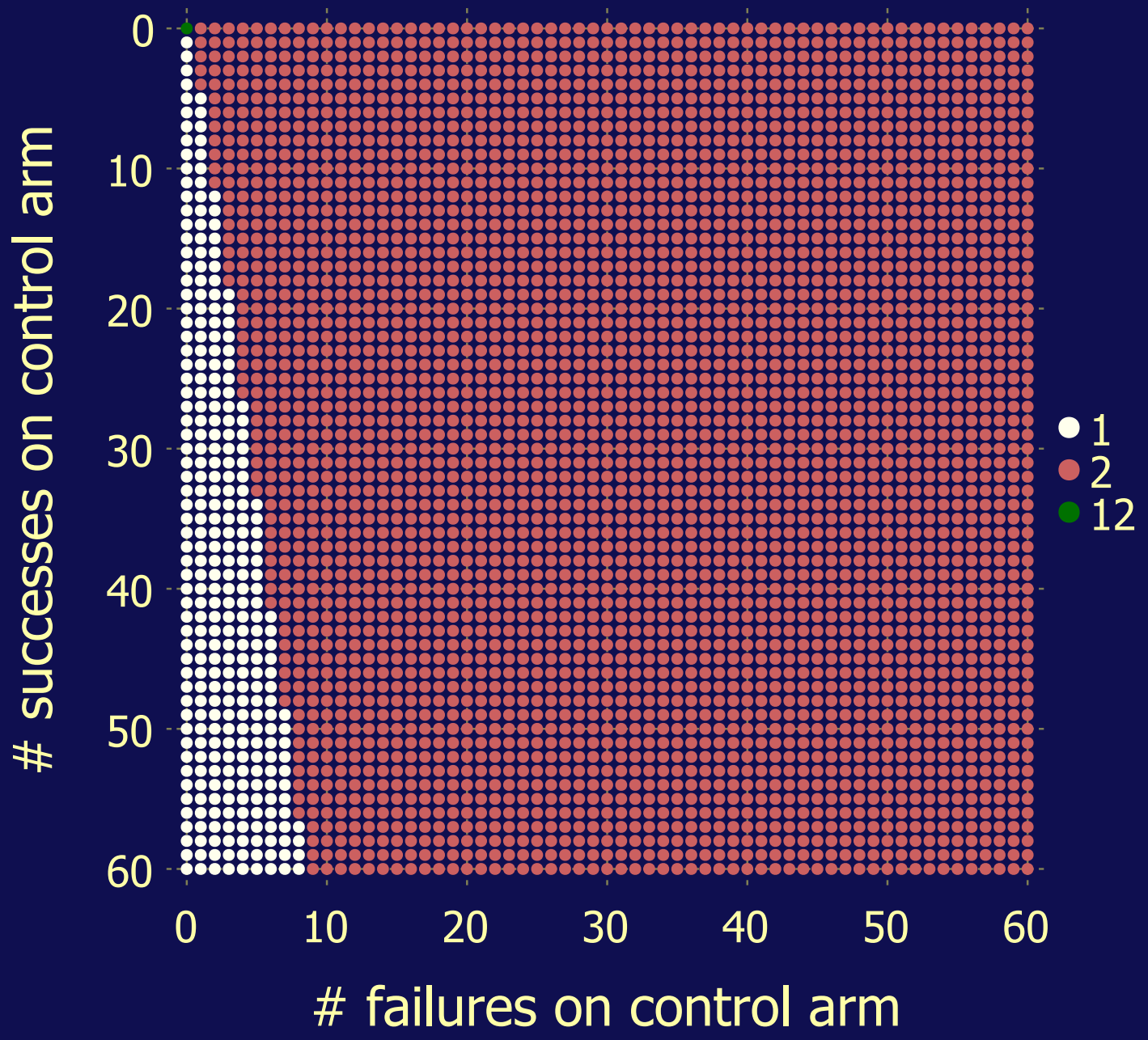
Relative Decrease in EPOF



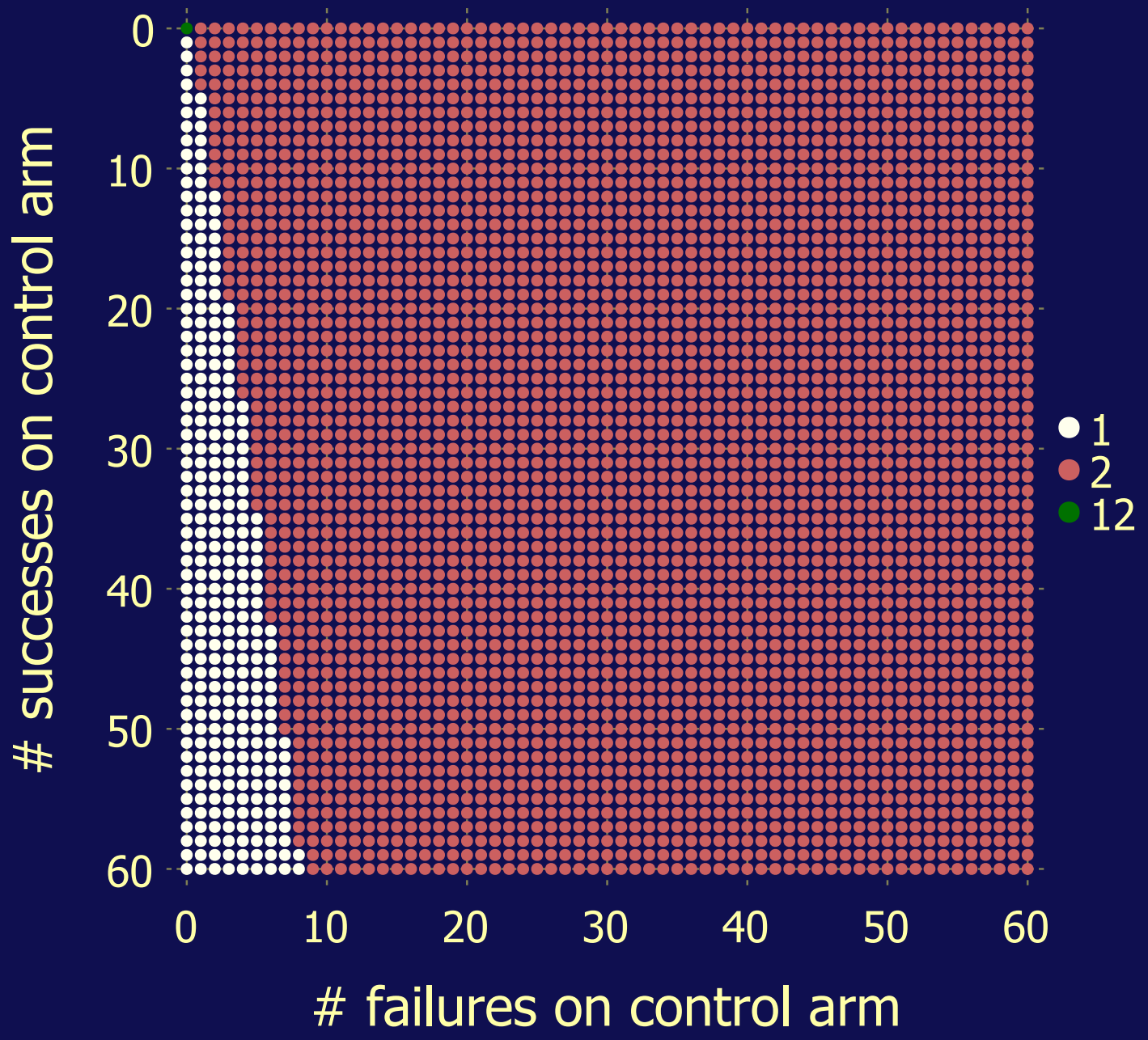
Introducing a Novel Arm

- Now we present the effect of increasing population size
  - ▷ is the novel allocated to the first patient?
- Sample size T affected by the recruitment rate and the number of competing arms
- Population size P affected by the timing of development of a better treatment in future
- Both affected by the incidence rate and prevalence of the disease

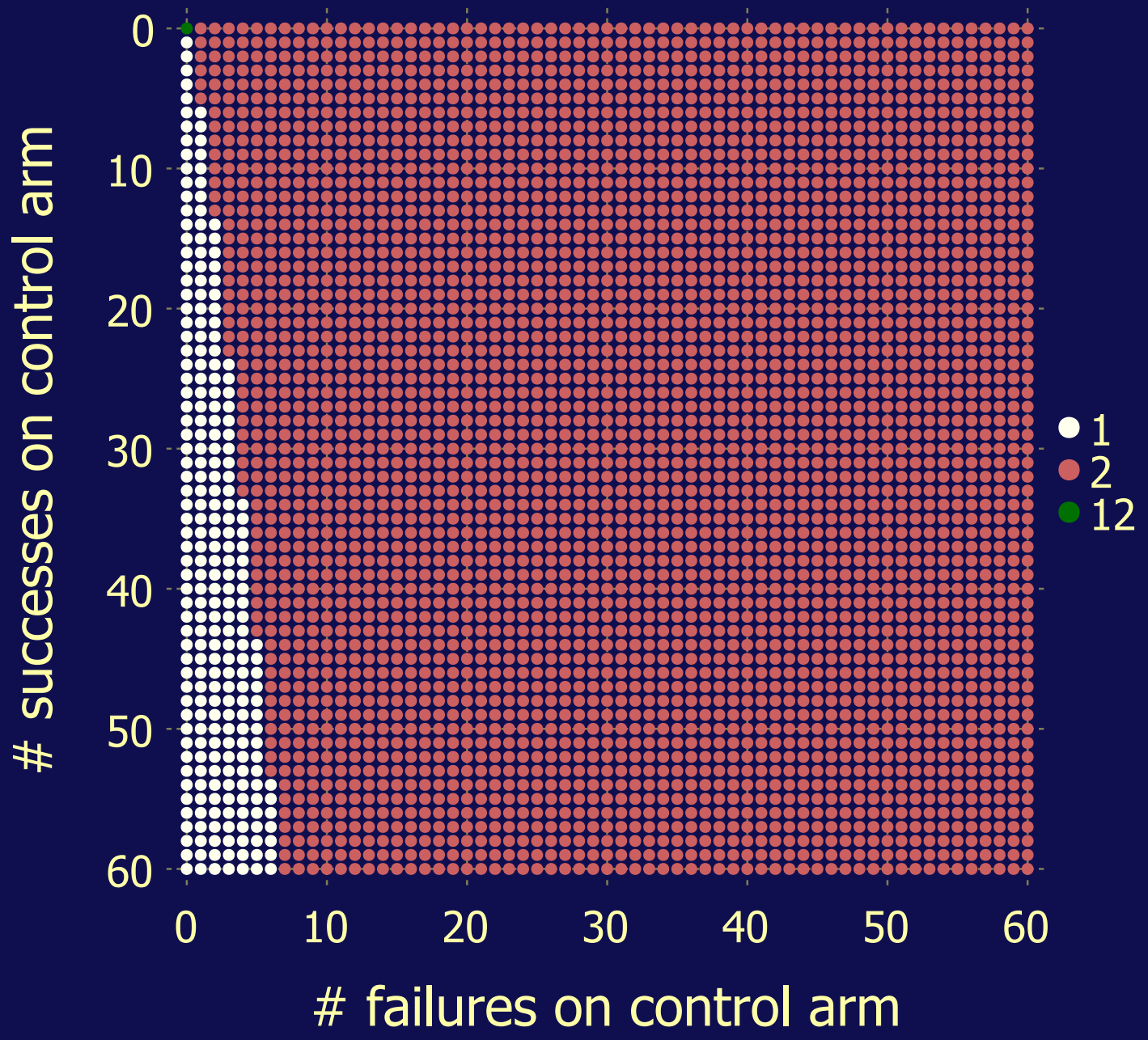
$T = 120, P = 0$: Optimal Allocation



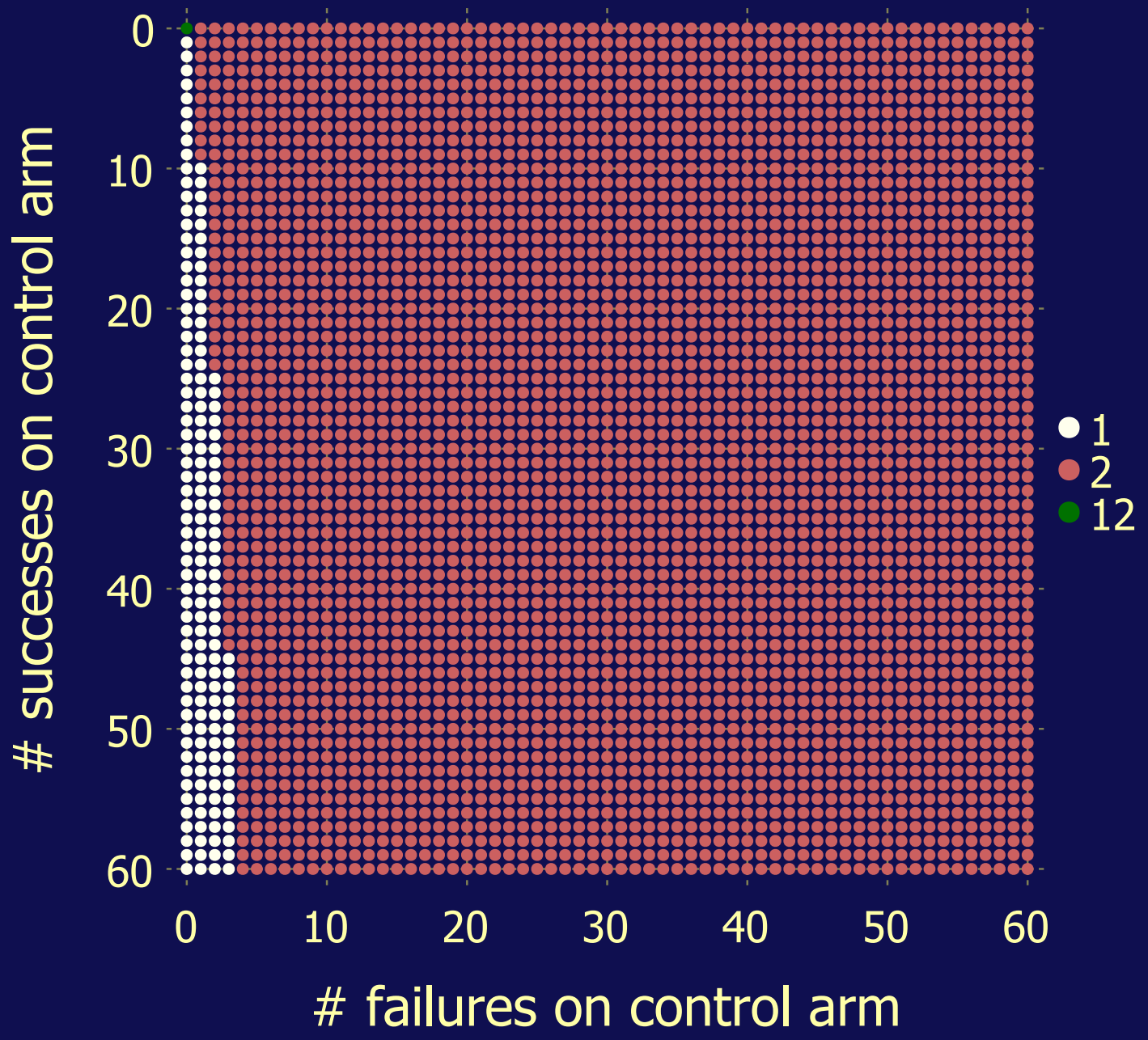
$T = 120, P = 10$: Optimal Allocation



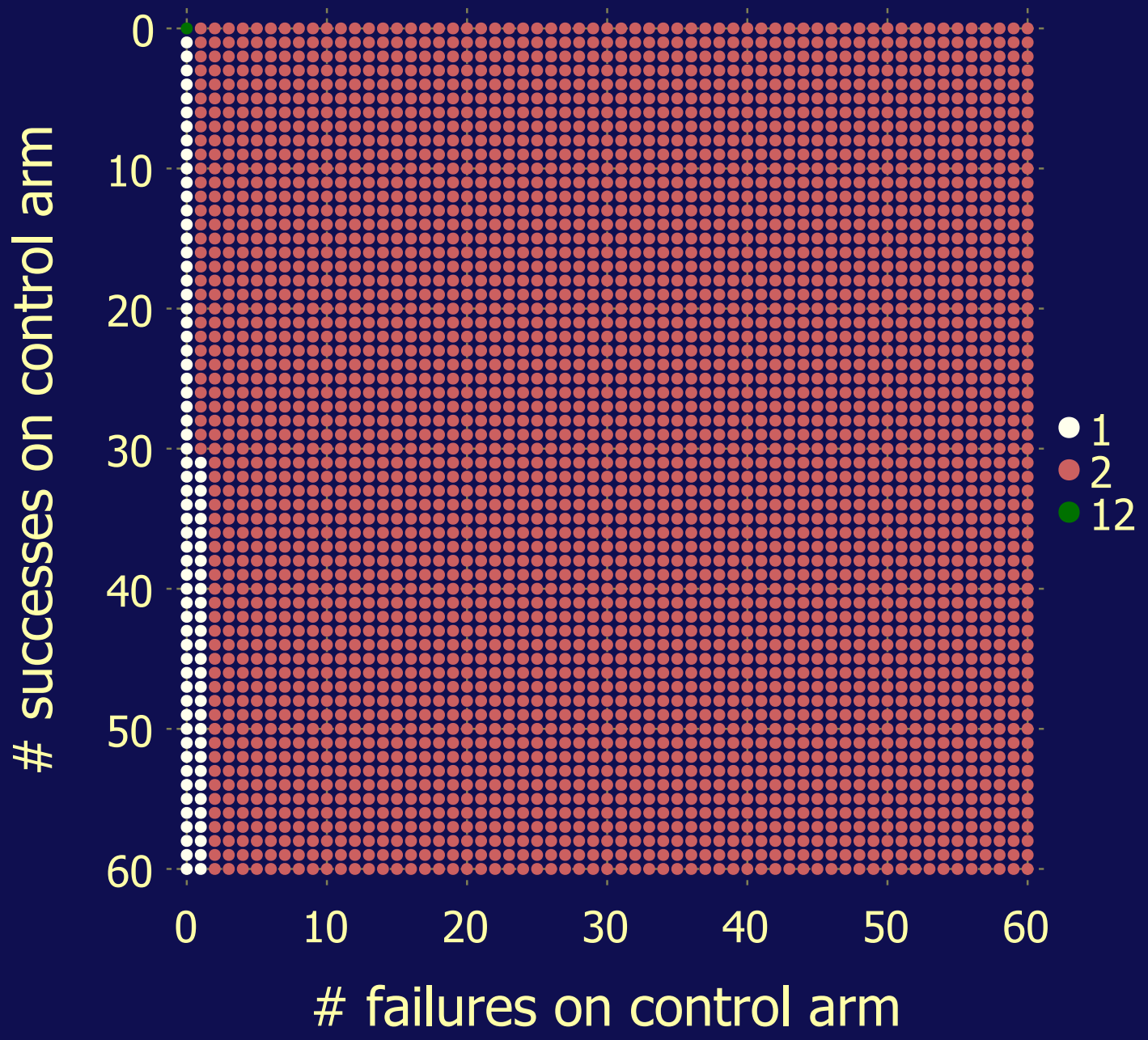
$T = 120, P = 100$: **Optimal Allocation**



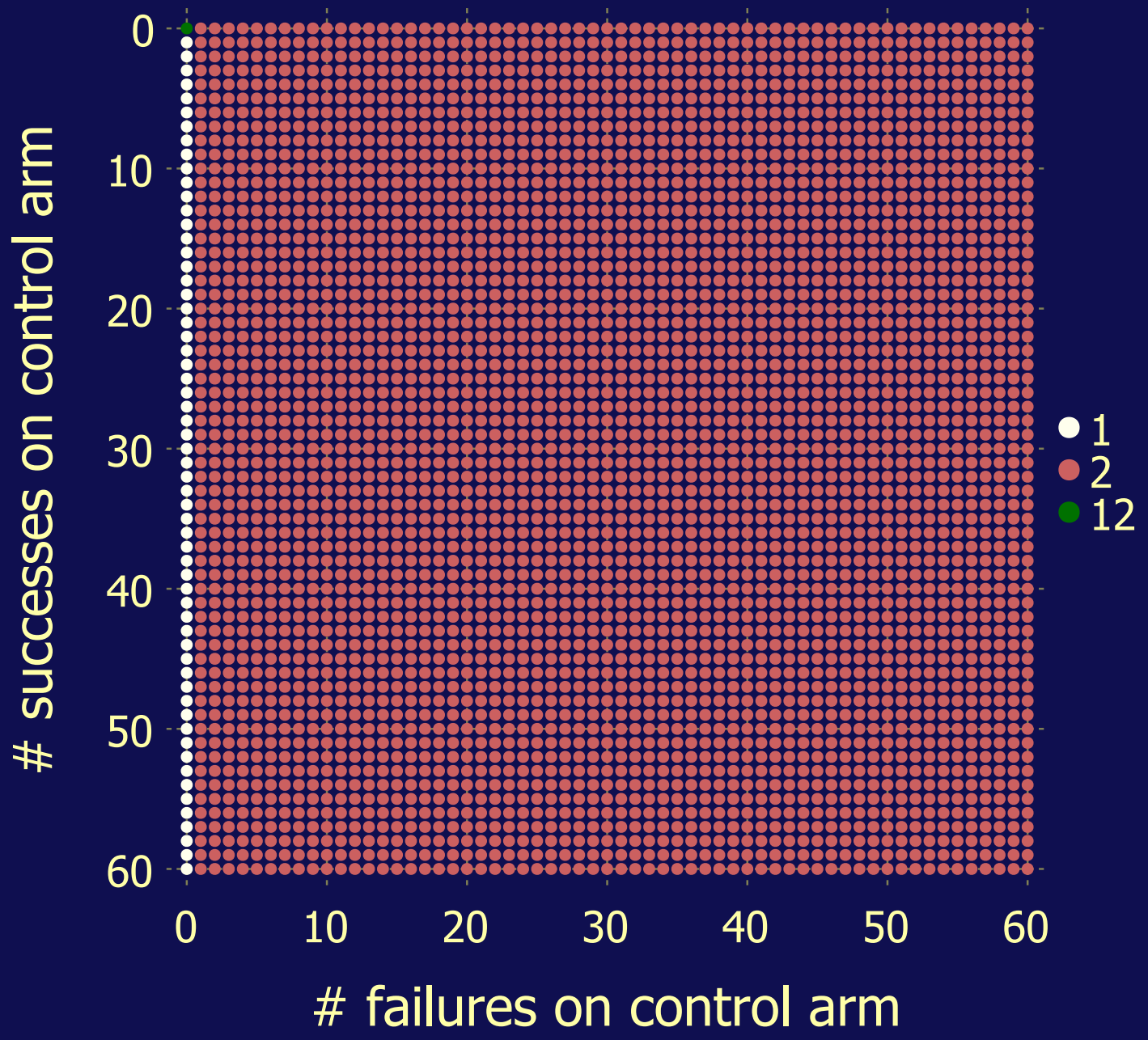
$T = 120, P = 1,000$: Optimal Allocation



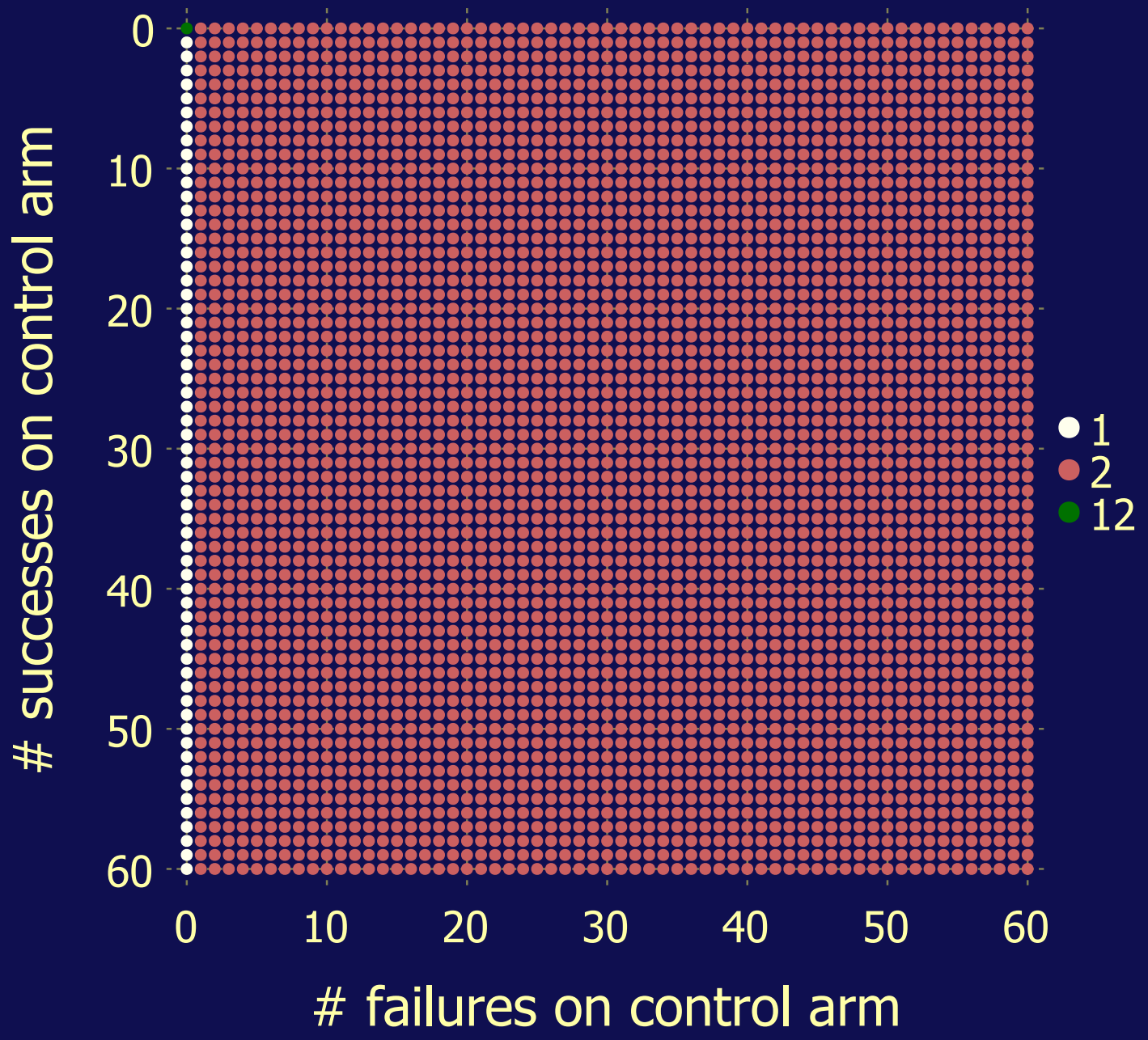
$T = 120, P = 10,000$: **Optimal Allocation**



$T = 120, P = 100,000$: **Optimal Allocation**



$T = 120, P = 1,000,000$: Optimal Allocation



Conclusions

- Small number of observations on the control arm is significantly better than nothing, and often enough
- Generally unless we have a control treatment that is extremely effective, from a health-benefit point of view we would want to add a new one to perpertual trial
- But if trial size is rather limited, it may not be worth adding a new treatment even if the control is moderately effective
- The size of the out-of-trial population makes a difference to in what situations we would want to experiment with a new treatment

Future Research Directions

- Computational reasons mean it is difficult to look at larger trials ($T > 1,000$) or trials with more arms
  - ▷ might use index policies
- Instead of looking at the first patient only, we could look at all in-trial patient allocation
- Effect of arm-branching due to biomarker subgroups
- We present a somewhat idealised scenario
  - ▷ to what extent these results hold in more traditional RCTs?

Take-Home Message

- Health benefit should be calculated and reported as one of the operating characteristics in every trial

Thank you for your attention