

## Introduction

There are around 52,000 new cases and over 12,000 deaths from prostate cancer every year in the UK. Over the last 18 years, almost 12,000 people volunteered to help researchers improve these statistics by taking part in one of the largest ever prostate cancer clinical trials: STAMPEDE.

STAMPEDE aimed to find the best way to treat people with -newly diagnosed advanced prostate cancer. Recruitment opened in 2005 in hospitals across the UK and later in Switzerland.

Unlike a traditional clinical trial that typically tests one new treatment at a time, STAMPEDE tested multiple new treatments at once, while comparing each of them against one shared control group who received the best currently available treatment for prostate cancer. STAMPEDE also added new treatments into the trial over time and stopped assessing other treatments early when they didn't work so well. Throughout the whole trial, all participants received the best available standard-of-care as a minimum – including those who were allocated the new treatments as well.

STAMPEDE's innovative design helped deliver results and make new treatments available to patients more quickly. In 20 years, results from STAMPEDE have directly led to changes in clinical practice several times, including from the docetaxel, abiraterone and radiotherapy comparisons.

This kind of progress may have taken many decades if the research was carried out in smaller, separate clinical trials. And none of it would have been possible without the 12,000 people who volunteered to take part in STAMPEDE.

Many of these were assigned to new treatments that turned out to improve prostate cancer survival. While others may not have benefited personally from taking part in STAMPEDE, they have improved treatment for the thousands of people who are diagnosed with prostate cancer every year, all around the world.

This booklet summarises the most impactful findings from STAMPEDE so far, and how these results have led to better care and more time with loved ones for people affected by prostate cancer.

# A BRIEF HISTORY OF STAMPEDE

**2005: STAMPEDE opens**

**2003: New trial design**

Researchers introduce the new multi-arm multi-stage clinical trial design to be used in STAMPEDE.

**2010: First Swiss patient**

**2005: First UK patient**

**2012: Celecoxib**

Adding celecoxib to standard hormone therapy does not improve survival of men with prostate cancer. Recruitment stops early for this group but existing participants are followed for several more years.

**2015: Docetaxel**

Adding docetaxel to standard hormone therapy helps men with prostate cancer that has spread to other parts of the body live longer.

**2016: Docetaxel NHS approval**

NHS approves the use of docetaxel in combination with hormone therapy for men with prostate cancer that has spread.

**2017: Celecoxib follow-up**

Follow-up data reveals that adding celecoxib to standard hormone therapy helps men with prostate cancer which has spread live longer, but not those whose cancer has not spread.

**2017: Abiraterone**

Adding abiraterone to standard hormone therapy helps men with prostate cancer that has spread live longer.

**2018: Radiotherapy**

Radiotherapy helps men with prostate cancer that has spread only to a few places around the body to live longer.

**2018: "Trial of the Year"**

STAMPEDE wins "Trial of the Year Award" from the Society for Clinical Trials.

**2018: 10,000 participants**

**2019: Docetaxel follow-up - metastatic**

Follow-up data confirms the long-term survival benefit of adding docetaxel to standard hormone therapy for men with prostate cancer that has spread.

## 2020: Radiotherapy NHS England approval

NHS England approves the use of radiotherapy for men with cancer that has spread only to a few places around the body.

## 2022: Abiraterone follow-up

Follow-up data confirms the survival benefit of adding abiraterone to standard hormone therapy for men with prostate cancer that has spread.

## 2023: Abiraterone NHS Scotland approval

NHS Scotland approves use of abiraterone in men with prostate cancer which has not yet spread but is at high risk of spreading.

## 2023: Abiraterone & enzalutamide

Adding abiraterone to standard hormone therapy at early stages helps men with advanced prostate cancer live longer, but there are no extra benefits of adding enzalutamide as well.

## 2024: tE2 patches - non-metastatic

Transdermal oestradiol patches are as good as standard hormone therapy injections at treating non-metastatic prostate cancer, with a slightly different side-effect profile.

## 2025: More results still to come...

## 2022: Docetaxel follow-up - non-metastatic

Follow-up data confirms that adding docetaxel to standard hormone therapy helps men with prostate cancer that has not spread to live longer, without their disease returning or getting worse.

## 2022: Radiotherapy follow-up

Follow-up data confirms the survival benefit of adding radiotherapy to standard hormone therapy for men with prostate cancer that has spread only to a few places around the body.

## 2023: Recruitment ends

STAMPEDE finishes recruiting new participants with 11,992 men enrolled.

## 2024: Metformin - metastatic

Metformin does not significantly improve how long men with metastatic prostate cancer live, but does reduce some side-effects of standard hormone therapy.

## 2024: Abiraterone NHS England & Wales approval

NHS England and Wales approve use of abiraterone in men with prostate cancer which has not yet spread but is at high risk of spreading.

## Docetaxel

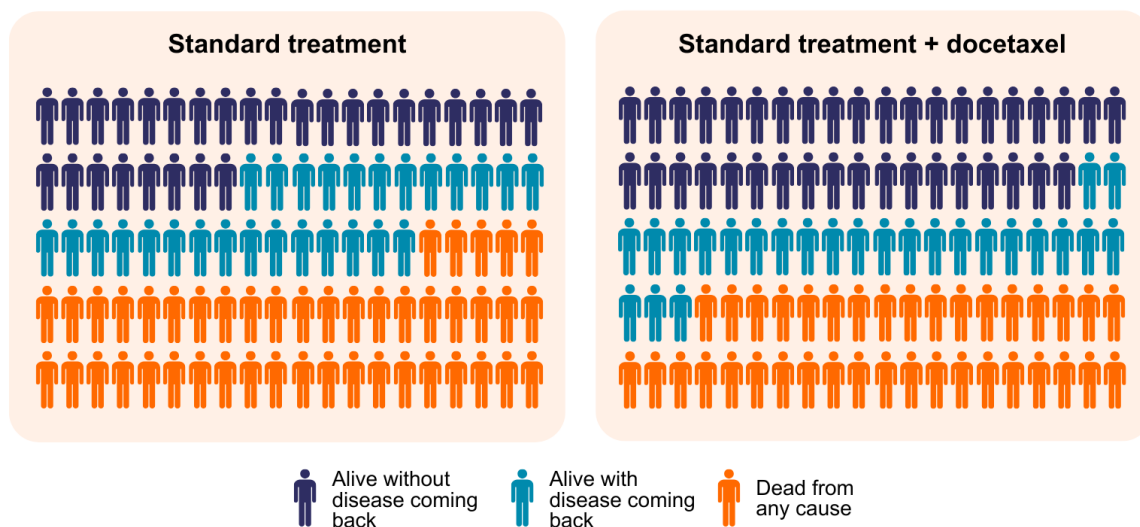
STAMPEDE's first big win came in 2015, with results from the trial's docetaxel comparison.

Docetaxel is a chemotherapy drug, which doctors already prescribed to treat prostate cancer after hormone therapy had stopped working. But in STAMPEDE, researchers looked at using it earlier, when men are first starting long-term hormone therapy.

The trial found that giving docetaxel upfront helped men with advanced prostate cancer live longer.

On average, men who received docetaxel on top of standard hormone therapy lived 10 months longer than those who had standard hormone therapy only. Docetaxel was particularly helpful for men whose cancer had spread to other parts of the body, adding 22 months to their lives on average compared with standard treatment alone.

### After 5 years...



Men assigned to docetaxel had some additional side effects compared to those on standard treatment, but these were usually manageable and didn't last long. Very few patients had to stop taking docetaxel because of side effects.

Following publication of the STAMPEDE docetaxel results, as well as passionate campaigning by the prostate cancer community, the UK's National Institute for Health and Care Excellence (NICE) officially added docetaxel to its guidelines for treating newly diagnosed advanced or high-risk prostate cancer. It soon became available on the NHS as part of the standard-of-care.

To properly evaluate the long-term impact of docetaxel, it was important to continue following trial participants for a few more years.

Follow-up results confirmed that upfront docetaxel helped people whose prostate cancer had already spread live longer. For those whose cancer had not yet spread when they joined STAMPEDE, docetaxel did not influence how long they lived, but did reduce the risk of the cancer spreading, returning or worsening within five years.

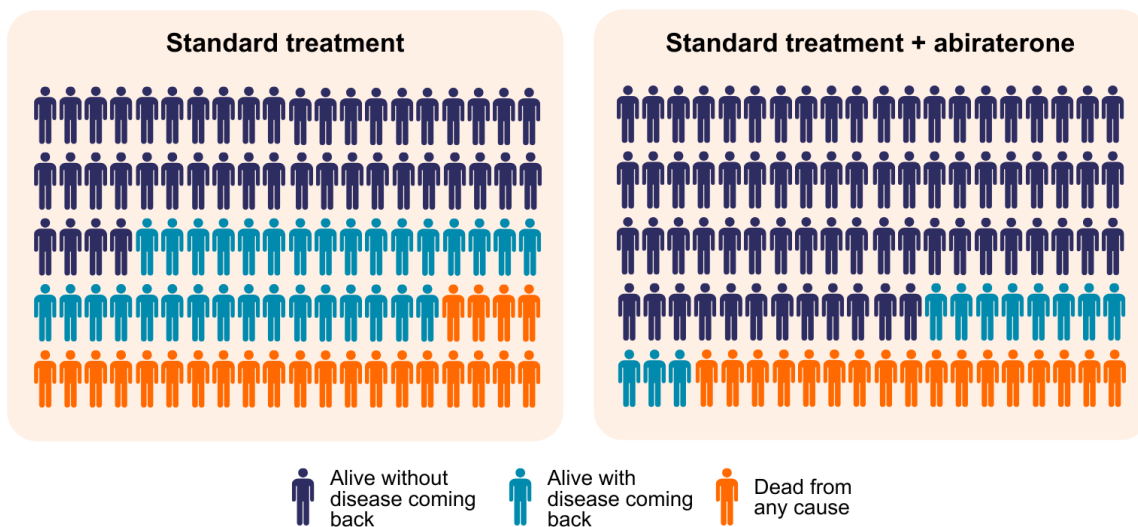
## Abiraterone

The first additional treatment introduced into STAMPEDE was abiraterone (also known as abiraterone acetate or Zytiga), a newer type of hormone therapy with a slightly different way of working. It is given alongside a steroid to reduce side effects.

At the time STAMPEDE's abiraterone arm opened in 2012, doctors usually saved the drug for people whose prostate cancer had already spread and when hormone therapy had stopped working. In STAMPEDE, researchers looked at using abiraterone earlier, at the start of long-term hormone therapy.

In 2017, the trial found that giving abiraterone upfront helped people with advanced prostate cancer to live longer.

### After 3 years...



On average, an extra seven people out of every 100 were still alive three years after joining the trial if they had abiraterone on top of standard hormone therapy, compared with those who received standard treatment alone. Abiraterone also helped reduce the risk of the cancer spreading, returning or worsening. Long-term follow-up results published in 2022 confirmed these findings.

Abiraterone did result in some extra side effects compared to standard hormone therapy alone, but these were generally manageable.

STAMPEDE also looked specifically at the benefits of abiraterone for people whose prostate cancer had not yet spread but was at high risk of doing so. The team found that abiraterone lowered the chance of the cancer spreading. Not only that, but taking abiraterone for two years was enough to help this group live longer.

In January 2023, NHS Scotland took a big step forward and approved the use of abiraterone along with standard hormone therapy at the start of treatment. After much campaigning, NHS England and Wales followed suit in December 2024. Abiraterone is now accessible across the whole UK for people with newly diagnosed high risk prostate cancer that is still responding to standard hormone therapy.

## Docetaxel or Abiraterone?

STAMPEDE found that docetaxel and abiraterone can both help people with advanced prostate cancer live longer. But which one is best?

To help people decide which treatment is right for them, researchers directly compared STAMPEDE participants assigned to each of these drugs.

There was no evidence of a difference in survival between the docetaxel and abiraterone groups. But when researchers asked about their pain, tiredness, anxiety, and how they were coping with day-to-day activities, they found that people taking abiraterone had better quality-of-life than those taking docetaxel.

Currently, both treatments are available to men starting long-term hormone therapy in the UK and further research is exploring whether there are benefits to taking both abiraterone and docetaxel.

## Radiotherapy

Radiotherapy uses high-energy radiation, similar to x-rays, to kill cancer cells. At the start of STAMPEDE, many participants whose prostate cancer had not spread when they joined the trial already received radiotherapy. But this was not the case for everyone.

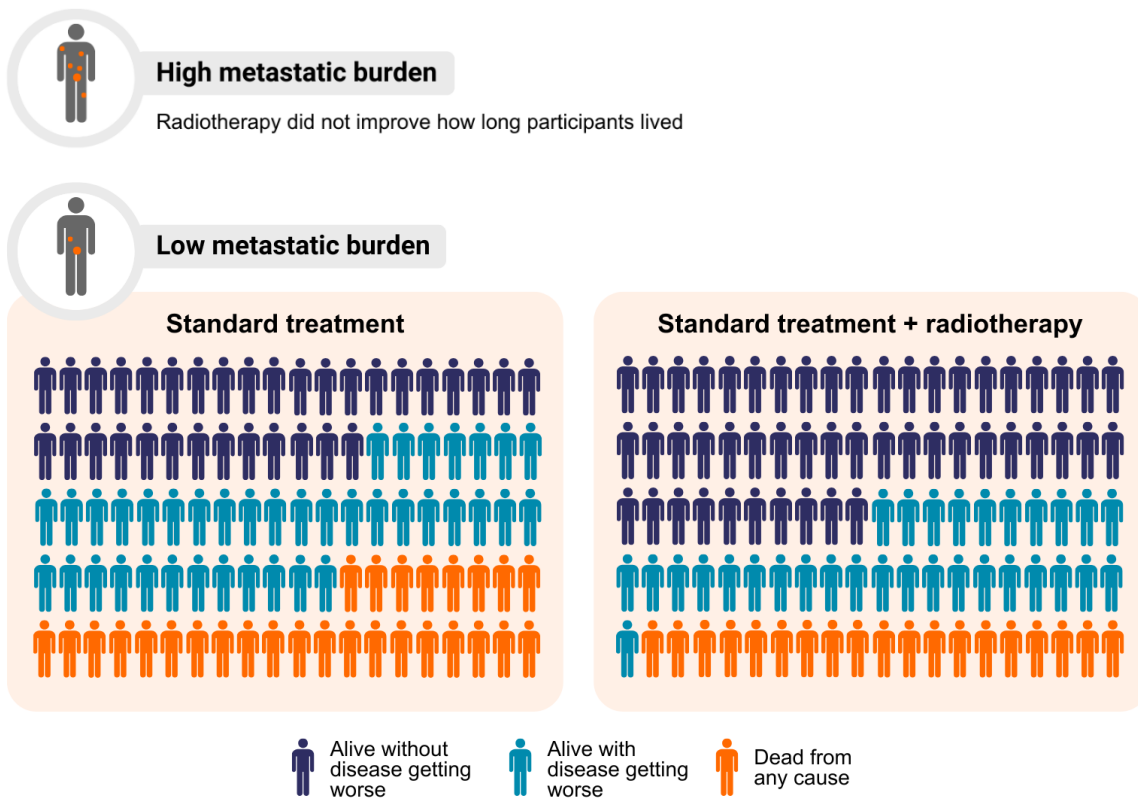
While STAMPEDE ran, another trial called PR07 reported that radiotherapy helped people live longer if their prostate cancer had not spread. Radiotherapy soon became part of the standard-of-care for people whose disease has not spread.

But researchers were still unsure about the benefits of radiotherapy when the cancer had already spread at the time of diagnosis. Many doctors thought there was no point in targeting the prostate itself once the cancer was present elsewhere in the body.

STAMPEDE started testing radiotherapy in this group in 2013. Anyone who joined STAMPEDE after 2016 could also have docetaxel when this became part of standard care.

On average, radiotherapy made no difference to how long people lived. But the STAMPEDE team had also planned to explore the data in finer detail, which told a different story.

### After 3 years...



If the cancer had spread significantly at the time of diagnosis, adding radiotherapy did not improve life expectancy any more than standard treatment. But if the cancer had spread only a bit beyond the prostate, radiotherapy did help them live longer.

Radiotherapy also helped delay the disease getting worse and did not appear to add severe side effects.

STAMPEDE changed many doctors' attitudes towards radiotherapy for prostate cancer that has spread. Unlike many new cancer drugs tested in clinical trials, radiotherapy is a simple and relatively cheap treatment that was already available in most parts of the world.

In 2020, the NHS officially added radiotherapy to its standard treatment for prostate cancer that has spread to a small number of places in their body.

Long-term follow-up results confirmed these findings in 2022, showing that an extra 12 people out of every 100 lived for at least five years after being diagnosed if they had radiotherapy. Radiotherapy also reduced the chance of complications in the bowel and bladder caused by spread of the cancer.

## Metformin

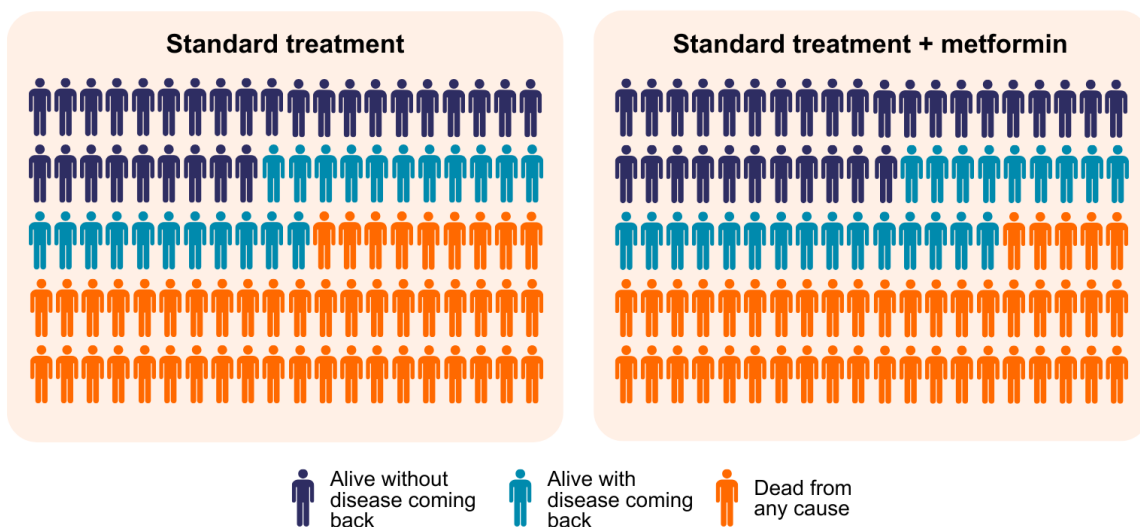
Standard hormone therapy can cause changes to the body's metabolism, leading to side-effects such as weight gain and insulin resistance. These may in turn lead to diabetes and an increased risk of heart disease, stroke and other health problems in the future.

Metformin is a tablet drug currently commonly used to treat type 2 diabetes, which affects the way the body processes fats and sugars. Previous studies have suggested that metformin may prevent prostate cancer from growing and spreading further in the body.

The STAMPEDE team wanted to find out if adding metformin to standard hormone therapy could improve how long people lived. The trial also aimed to see if metformin could prevent some of the side-effects of hormone therapy.

The metformin comparison opened in 2016. Only people without diabetes could join this comparison, therefore all people who wished to take part needed to have a blood test to check for diabetes first. The first results from the metformin arm were released in September 2024, looking at participants whose cancer had already spread when they joined the trial.

### After 5 years...



STAMPEDE found that taking metformin alongside standard hormone therapy did not significantly

improve how long people lived, compared to standard hormone therapy alone. On average, participants taking metformin lived six months longer than those who had standard treatment only. But the difference between groups was not big enough to be sure that this was not due to chance.

There was evidence to suggest that metformin may be more beneficial for people whose cancer had spread more at the time of diagnosis, compared to those whose cancer had not spread much. However, more research is required to confirm and understand this finding.

Metformin did however lessen some of the common side-effects of standard hormone therapy, including weight gain, high cholesterol and high blood sugar. This may help reduce the risk of long-term health problems in the future.

Metformin is a cheap and readily available drug, but the current drug license does not cover prostate cancer, so it may not be immediately available within the NHS for use in people with prostate cancer.

## Transdermal oestradiol (tE2) patches

Prostate cancer which has either already spread or is at high risk of doing so is usually treated with androgen deprivation therapy. This type of hormone therapy is usually given using injections of LHRH analogues, which lower levels of testosterone in the body.

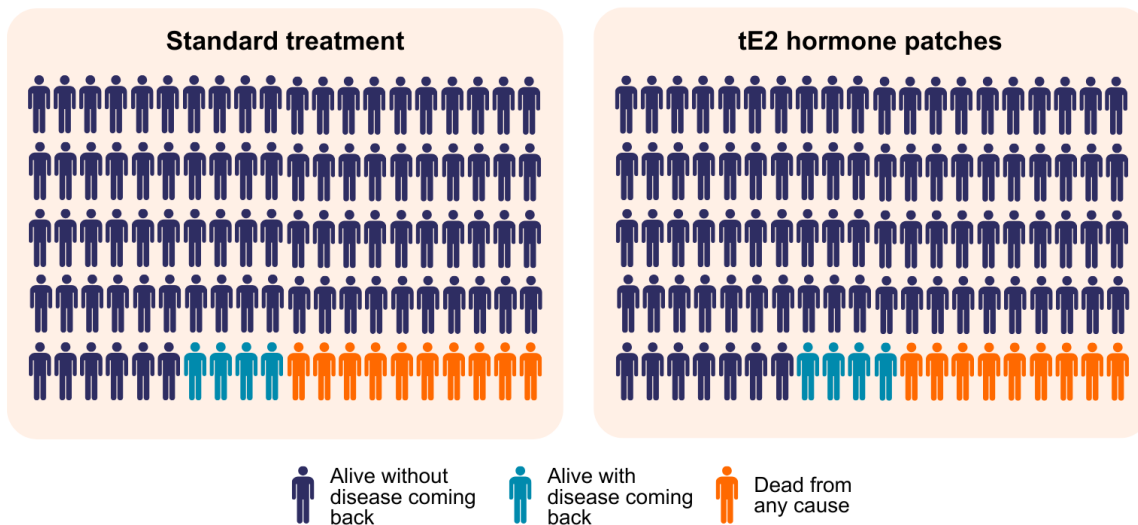
Unfortunately, standard hormone therapy injections can cause a range of long-term side effects, including thinning of the bones, which may lead to them becoming fragile (osteoporosis) and more likely to break. Another common side effect is hot flushes, which can impact quality of life.

STAMPEDE tested an alternative way of giving hormone therapy through transdermal oestradiol (tE2) hormone patches. They contain a type of hormone called oestradiol, which can enter the body by passing through the skin. Like LHRH analogues, oestradiol lowers the body's testosterone levels. Unlike injections, these patches can be applied at home without needing to visit a clinic.

The team wanted to know if tE2 patches can treat prostate cancer in a similar way to standard hormone therapy injections, without causing some of the side effects. The tE2 comparison of STAMPEDE was designed to be analysed together with data from another clinical trial called PATCH.

The first results, released in September 2024, only included participants whose prostate cancer was high risk, but had not spread beyond the prostate at the time they joined the trial.

## After 5 years...



After following participants for at least three years and some for over 15 years, the trials found that hormone patches were as good as standard-of-care hormone therapy injections at treating non-metastatic prostate cancer.

There were some differences in side-effects between the two groups. Hot flushes were much less common among those using patches. However, participants using hormone patches were more likely to experience breast tissue swelling (gynaecomastia) than those receiving standard hormone therapy injections.

Hormone patches could increase the treatment options available for people with prostate cancer in the future, allowing them to choose a hormone therapy approach that is best suited to them individually, in terms of the side-effects profile and how the treatment is delivered. Results will follow showing the effects of hormone patches in those whose cancer has already spread when they begin long-term hormone therapy.

## STAMPEDE publications

<http://www.stampetrial.org/media-section/publication-repository/>